The New England
Journal of Medicine

Copyright, 1952, by the Massachusetts Medical Society

Volume 247 DECEMBER 11, 1952 Number 24

MITRAL STENOSIS WITH LONG-LASTING CONGESTIVE HEART FAILURE OR AURICULAR FIBRILLATION*

DONALD E. LOVE, M.D.,† AND SAMUEL A. LEVINE, M.D.‡

BOSTON

THE outlook for the patient with mitral stenosis in whom objective evidence of congestive heart failure or auricular fibrillation has already developed has generally been considered grave. Studies have indicated that the average survival after onset of congestive heart failure or auricular fibrillation is in the range of three to five years.[1-3] However, observation of patients in the cardiac clinic of the Peter Bent Brigham Hospital who have survived for as long as a quarter of a century after the onset of these complications has posed a question of the frequency of such prolonged survival. Accordingly, the records of the Hospital were analyzed. Patients with mitral stenosis who had been seen between 1913 and 1946 and who had died during one of the admissions to the hospital were studied. The active membership of the outpatient cardiac clinic was also scanned. From the resulting group of records, 65 cases were found in which the patient had survived nine or more years after the onset of objective evidence of congestive heart failure or permanent auricular fibrillation. In the great majority of these 65 cases congestive heart failure followed the development of auricular fibrillation. In some cases adequate digitalis therapy and other measures had controlled the symptoms of congestion so well that gross evidence of failure did not appear until some years after auricular fibrillation had developed. In a small group, mainly those with tricuspid stenosis as well as mitral stenosis, a normal sinus rhythm was known to be present for some years after congestion first appeared, though in all cases auricular fibrillation or flutter (1 case) ultimately ensued.

The onset of auricular fibrillation was determined by the first detection of a gross arrhythmia on auscultation, or in many cases by electrocardiographic study. The symptom of palpitation per se was not regarded as sufficient evidence for the diagnosis of this arrhythmia. It is obvious that in some cases auricular fibrillation must have been present for a longer period than we were able to identify. The first development of congestive heart failure was not so easily ascertained. A simple history of dyspnea on exertion was not sufficient. In fact, practically all these patients with mitral stenosis had dyspnea on effort for long periods before they displayed the more definitive features of congestion that we required in dating the onset of heart failure. The criteria that we used to time the onset of failure were paroxysmal nocturnal dyspnea, true orthopnea, persistent pitting edema of the ankles, hepatomegaly and hydrothorax. A few patients with isolated congestive heart failure with pregnancy, thyrotoxicosis or possibly active rheumatic fever who then lived a period of years free from failure were not included. Thus the patients with congestion were in greater or lesser degrees of real or gross decompensation during the period under study.

A simple analysis of the average duration of life after congestive heart failure or fibrillation had developed in cases of mitral stenosis was made for patients dying at the Peter Bent Brigham Hospital from 1913 to 1926 as contrasted with the period from 1926 to 1946. The figure for the former was two and one-quarter years and for the latter three and three-quarters years, a gain in longevity of a year and a half. The obvious inference is that the treatment of heart failure has improved and that patients now live longer after the onset of failure. Further evidence of the change that has taken place in recent decades is the report of Davis and Weiss,[4] who found that of 164 patients with rheumatic heart disease examined after death in the Boston City Hospital from 1905 to 1929, only 4 per cent survived congestive heart failure for ten years or more. In the present study 510 patients with mitral stenosis died in the Peter Bent Brigham Hospital, and 41, or 8 per cent, were in the group of long survivors. Among 164 patients with mitral stenosis who were being seen in the outpatient cardiac clinic between 1940 and 1942 and whose subsequent course is known, 22 (13 per cent) lived or are living

*From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.

†Research fellow in medicine, Harvard Medical School; assistant in medicine, Peter Bent Brigham Hospital.

‡Clinical professor of medicine, Harvard Medical School; physician, Peter Bent Brigham Hospital.

nine or more years after the onset of auricular fibrillation or of congestive heart failure; this figure is probably more representative of present-day practice than the former, which included some patients dying before the era of mercurial diuretics, salt restriction and antibiotics. In general, it appears that 10 to 13 per cent of all cases of mitral stenosis will fall into the group with prolonged survival.

Fourteen patients in this group were male, and 51 were female. Since, in mitral stenosis in general, females predominate at a ratio of about 2:1, this proportion of nearly 4:1 suggests that women are likely to survive longer.

Forty-one of the group of 65 are known to have died, and 26 of these were examined after death. The average age at death was forty-nine and four-tenths years for the deceased group, and that of those living was fifty-eight years at the time of their last visit. The average age for the entire group was fifty-three years, with no significant sex difference.

Thirty-nine patients — 71 per cent of the men and 57 per cent of the women — gave a definite past history of rheumatic fever. Four others had a probable history of previous rheumatic infection. An average interval of thirty-six years elapsed between the initial attack of rheumatic fever and death. The average interval from the occurrence of rheumatic fever to the onset of congestive heart failure or auricular fibrillation was twenty-three and twenty-five years respectively. The average duration of congestive heart failure for the entire group of 65 cases was ten and six-tenths years, and that of auricular fibrillation was twelve and eight-tenths years.

Valvular Lesions

The various types of valvular lesions and their relation to the age at death or last visit, duration of congestive heart failure and duration of auricular fibrillation are presented in Table 1. These data are of interest in that patients with tricuspid and mitral stenosis were about one decade younger and had a somewhat shorter duration of auricular fibrillation than the others.

Table 1. *Relation of Valvular Lesion to Course.*

Valve Affected	No. of Cases	Age at Last Visit yr.	Duration of Failure yr.	Duration of Fibrillation yr.
Mitral	34	52.2	10.0 (30 cases)	13.0 (31 cases)
Mitral and aortic	16	54.4	11.7 (10 cases)	12.3 (16 cases)
Mitral, aortic and tricuspid	9	49.5	10.9 (6 cases)	13.5 (9 cases)
Mitral and tricuspid	6	43.3	10.4 (6 cases)	11.3 (3 cases)
Totals	65	53.3	10.6 (52 cases)	12.8 (59 cases)

Hypertension

Thirty-two patients (50 per cent) had average blood pressures above 150 systolic, 90 diastolic, and this finding occurred with equal frequency among male and female patients. The average age at death or last visit was fifty-three and four-tenths years, slightly above that for the patients without hypertension — fifty-one years. This suggests a protective role for hypertension, or it could be concluded that since hypertension becomes more prevalent with advancing years, any selection made on the basis of hypertension will be weighted toward the older ages. These data do not afford a reliable means of adequately assessing the role of hypertension in the progress of mitral stenosis. In some cases it has appeared that as hypertension developed the degree of congestive heart failure previously present, or its refractoriness to treatment, was subsequently lessened. We are also impressed by the fact that many women do surprisingly well for long periods with mitral stenosis and hypertension, a peculiarity discussed in a previous communication.[5]

Angina Pectoris

Sixteen patients were thought to have angina pectoris; of these only 1 was male. Fourteen of the group also had systemic hypertension. There were 2 cases of myocardial infarction, both in female patients. In 1, an old posterior myocardial infarction was discovered at autopsy, and in the other there was electrocardiographic evidence of acute anterior myocardial infarction. The duration of congestive heart failure and auricular fibrillation did not differ significantly from that of the group at large. The incidence of angina pectoris reported by Levine and Kauvar[6] in their series of patients with mitral stenosis ranged from 2.2 to 5.0 per cent, rather than the 25 per cent encountered here. However, it has been reported that angina pectoris is unusual with auricular fibrillation,[7,8] and all patients in this group had that form of arrhythmia. In spite of the facts that 2 patients had proved myocardial infarcts, that coronary arteritis is not infrequent as a result of rheumatic carditis, that hypertension was a frequent complication in this group and that the average age was fifty-three years, some other factor is probably responsible for the great frequency of angina in the female patients in this group. Some of the patients who were thought to have angina may represent cases of the syndrome recently described by Viar and Harrison.[9] Such patients with mitral stenosis have symptoms resembling angina that are thought to be due to increased pulmonary pressure rather than to coronary sclerosis.

Symptomatology

Women seem to experience dyspnea for a longer time and to manifest hematomegaly for a shorter

time than men. Significant hydrothorax was present at some time in 35 patients, occurring, as was to be expected, predominantly in the right side of the chest.[10, 11] Auricular fibrillation was ultimately found in all patients but 1, who showed auricular flutter. The average duration of auricular fibrillation was twelve and eight-tenths years. The duration of this arrhythmia and the number of cases manifesting it in patients with different combinations of valvular involvement can be seen in Table 1. Hypertension was recorded in half these patients. It is of interest that subacute bacterial endocarditis was not the cause of death in any case, nor was it found in a single case among the 26 examined at autopsy. This supports the well known concept that bacterial endocarditis is a rare development in the course of long-standing congestive heart failure or auricular fibrillation.[12]

Cause of Death

The chief contributing cause of death was determined in each fatal case. Whereas all but 2 of the 41 patients who died (95 per cent) were in congestive heart failure at the time of death, and had been in failure on an average of eleven and a half years prior to death, only 29, or 70 per cent, could be considered to have died primarily as a result of heart failure. Seven (17 per cent) died of emboli — 4 of systemic and 3 of massive pulmonary emboli. Quinidine therapy was responsible for 2 cases (both deaths occurred in 1923), and lobar pneumonia for 2 others. The cause of death was uncertain in the final case.

Course among Survivors

Six of the 24 patients who did not die in this hospital are probably dead, judging from the data obtained at the last visit. The remaining 18 patients are still being seen at intervals in the cardiac clinic. Nine may be considered to be in fairly good condition in that they are able to work full or part time, never having had objective evidence of congestive heart failure though manifesting persistent auricular fibrillation for an average of fourteen and three-tenths years. An additional patient recently underwent mitral valvuloplasty despite the fact that she had had permanent auricular fibrillation for twenty-six years and congestive heart failure with each of four pregnancies in the preceding fourteen-year period. She is now doing a moderate amount of housework. The remaining 8 patients are severely handicapped by their cardiac status but are still able to attend the outpatient clinic. They have had an average duration of congestive heart failure of five and eight-tenths years, with fibrillation for sixteen and a half years.

Discussion

In everyday cardiac practice one encounters patients with mitral stenosis who have survived far beyond the expected span of life after the development of congestive heart failure or the onset of auricular fibrillation. The analysis of data from patients with mitral stenosis seen at the Peter Bent Brigham Hospital suggests that 10 to 13 per cent will survive nine or more years after the onset of congestive heart failure or auricular fibrillation. It is to be pointed out that patients under twelve years of age were not included in this study, since such patients are not usually admitted to this hospital.

The average age of the group of 65 patients (14 men and 51 women) analyzed in this study was older than that reported for patients with rheumatic heart disease in general. This discrepancy mainly stems from the fact that the group in the present study were "long survivors." It is of some interest that there was such a great preponderance of women.

Thirty-nine patients gave a definite past history of rheumatic fever. The average age at the time of the initial attack was seventeen years — about two years older than the average figures reported by Cohn and Lingg,[13] who found from a study of 12,000 patients with rheumatic heart disease admitted to New York hospitals that the average age at onset was fourteen and a half years for male and fifteen years for female patients. According to these authors, the later in life the initial attack occurs, the greater the age at death. However, Davis and Weiss,[4] in their smaller study of 369 cases of rheumatic heart disease, concluded that the duration of life after the onset of rheumatic fever was shorter for the patient having his first attack after the age of twenty-five than for the person with an initial attack before the age of ten.

Fifty per cent of the group were considered hypertensive. Hypertension has been thought to have a protective role in patients with mitral stenosis,[5] but this study afforded no opportunity to test the validity of this view.

Symptoms diagnosed as angina pectoris were present in 25 per cent of the group, all but 1 occurring in females. It is thought that the angina-like pain observed in patients with pulmonary arterial hypertension may have accounted for some cases in this category.

Analysis of congestive signs and symptoms revealed little difference between male and female patients except that the latter noted dyspnea on the average three years sooner and manifested hepatomegaly three years later than the male patients.

Congestive heart failure, present in 95 per cent of the group, was the principal cause of death in only 70 per cent of the 41 patients who died. Seventeen per cent of the group died as a result of pulmonary or systemic embolization.

An important practical question that will occur to the clinician who follows patients with mitral stenosis is whether one can in any way predict which one is more likely to fall into the group of long

survivors. At the onset it may be said that there appears to be no accurate method of prediction. The fact that tricuspid stenosis was present in a fourth of the patients in this series and occurs in only a tenth of all cases of rheumatic heart disease[14] makes it clear that patients with mitral and tricuspid stenosis are likely to survive longer than those without tricuspid stenosis.

The evidence that hypertension accompanying mitral stenosis acts favorably and renders such patients likely to survive longer is not certain. We have a strong clinical impression that this is so, but proof is not available. There is a third group, however, with neither tricuspid stenosis nor hypertension, but whose members become "long survivors."

The main purpose of this review is to call attention to a considerable group of patients with mitral stenosis who have lived for a great many years after some major handicap develops. To be sure, many of them are so incapacitated that they cannot work, but others are able to continue with moderate activities and to remain ambulatory, supporting themselves in a light or sedentary occupation. No doubt the present surgical treatment of mitral stenosis has been effective in improving the state of compensation in many cases and in restoring economic usefulness when ordinary medical measures have failed. However, in judging the indications for surgery and the duration of life after operation, the data presented here deserve consideration.

Summary and Conclusions

About 13 per cent of patients with mitral stenosis will survive nine or more years after the inception of gross objective evidence of congestive heart failure or auricular fibrillation.

There appear to be three groups of so-called "long survivors" — those with tricuspid stenosis, others with hypertension and a third miscellaneous group with neither of these factors.

These facts should be taken into consideration in an evaluation of the indications for and the results of valvuloplasty.

References

1. Cookson, H. Aetiology and prognosis of auricular fibrillation. *Quart. J. Med.* **23**:309-325, 1930.
2. Laws, C. L., and Levine, S. A. Clinical notes on rheumatic heart disease with special reference to cause of death. *Am. J. M. Sc.* **186**: 833-849, 1933.
3. DeGraff, A. C., and Lingg, C. Course of rheumatic heart disease in adults. II. Influence of type of valvular lesion on course of rheumatic heart disease. *Am. Heart J.* **10**:478-485, 1935.
4. Davis, D., and Weiss, S. Rheumatic heart disease. IV. Life history of severe form of disease. *Am. Heart J.* **10**:486-494, 1935.
5. Levine, S. A., and Fulton, M. N. Relationship of hypertension to mitral stenosis. *Am. J. M. Sc.* **176**:465-474, 1928.
6. Levine, S. A., and Kauvar, A. J. Association of angina pectoris or coronary thrombosis with mitral stenosis. *J. Mt. Sinai Hosp.* **8**: 754-764, 1942.
7. Libman, E. Clinical features of subacute streptococcus (and influenzal) endocarditis in bacterial stage. *M. Clin. North America* **2**: 117-151, 1918.
8. MacKenzie, J. *Angina Pectoris.* 269 pp. London: Oxford University Press, 1923. P. 95.
9. Viar, W. N., and Harrison, T. R. Chest pain in association with pulmonary hypertension: its similarity to pain of coronary disease. *Circulation* **5**:1-11, 1952.
10. McPeak, E. M., and Levine, S. A. Preponderance of right hydrothorax in congestive failure. *Ann. Int. Med.* **25**:916-927, 1946.
11. White, P. D., August, S., and Michie, C. R. Hydrothorax in congestive heart failure. *Am. J. M. Sc.* **214**:243-247, 1947.
12. Rothschild, M. A. Sacks, B., and Libman, E. Disturbances of cardiac mechanism in subacute bacterial endocarditis and rheumatic fever. *Am. Heart J.* **2**:356-374, 1927.
13. Cohn, A. E., and Lingg, C. Natural history of rheumatic cardiac disease: onset and duration of disease. *J. A. M. A.* **121**:1-8, 1943.
14. Smith, J. A., and Levine, S. A. Clinical features of tricuspid stenosis: study of trivalvular stenosis. *Am. Heart J.* **23**:739-760, 1942.

Correction. The word "intussusceptum" appearing in the ninth line of the first paragraph on page 501 of the article entitled "Intussusception: A review of experience at the Massachusetts General Hospital, 1937–1951," by Drs. Lawrence and Ulfelder, which appeared in the October 2 issue of the *Journal*, should be changed to read "intussuscipiens."

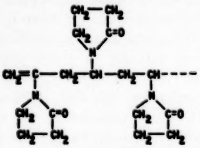
POLYVINYL PYRROLIDONE AS A PLASMA EXPANDER*

Studies on Its Excretion, Distribution and Metabolism

HERBERT A. RAVIN, M.D.,† ARNOLD M. SELIGMAN, M.D.,‡ AND JACOB FINE, M.D.§

BOSTON

POLYVINYL pyrrolidone (P. V. P., Periston or Kollidon), was proposed in 1940 as an effective nontoxic plasma substitute.¶ It is a synthetic, water-soluble, macromolecular polymer, dissolved in buffered physiologic saline solution in a concentration of 3.5 per cent, so as to be nearly isotonic and iso-oncotic with normal plasma (osmotic pressure equivalent to 400 to 450 mm. of water).



It was administered to large numbers of soldiers and civilians during the ensuing war years in Germany and since then in other European countries and in the United States. All early reports agreed that it was effective in the treatment of traumatic shock, and some investigators considered it nearly as good as plasma.[2-4] Later clinical experience suggested other important therapeutic benefits to be derived from its ability to bind dyes[5, 6] and bacterial toxins,[7-9] and to facilitate their excretion in the urine.

Histopathological studies in man[10, 11] and animals[12-14] revealed a transient histiocytosis and phagocytosis of P.V.P. by macrophages for several weeks after its administration. Clinical evidence of toxicity or of functional impairment of the liver or kidney was not found, except for elevation in sedimentation rate and an occasional case of transient albuminuria. The elevation in sedimentation rate, a general response of erythrocytes to all macromolecules, was found to parallel the serum concentration of P.V.P., and was reproducible in vitro.[15-17]

Since only 40 to 60 per cent of the polymer was excreted in the urine, mainly during the first two or three days after infusion, and no other significant portal of exit was demonstrable, it was tacitly assumed that the remainder of the P.V.P. was modified or degraded because none could be detected in the body by chemical methods after two to four weeks.

Despite the lack of evidence of deleterious effects of polyvinyl pyrrolidone in a large number of human recipients (over 500,000)[18] some ten years after its administration, it was considered necessary to determine how long the fraction not excreted in the first few weeks after administration remained in the body, its distribution and any possible toxic effects of long-term retention.

Because of the lack of sensitivity of the chemical methods of analysis for P.V.P., radioactive-tracer technics were employed to follow, with as much precision as possible, the immediate and ultimate disposition of all the injected material. P.V.P. labeled with either I^{131} or C^{14} was used.

METHODS

Radioactive P.V.P. was prepared by tagging with I^{131} in the following manner[19]: approximately 700 mg. of P.V.P. was dissolved in 20 cc. of distilled water and 2 cc. of 20 per cent sodium carbonate. In a separate beaker 1 to 5 millicuries of carrier-free NaI^{131} was diluted with 0.5 to 1.0 mg. of iodine in the form of sodium iodide solution (0.65 mg. per cubic centimeter). Ten cubic centimeters of a 1 per cent sodium nitrite solution was added, and finally 10 cc. of one-tenth normal solution of hydrochloric acid, swirled rapidly into the mixture of sodium iodide and sodium nitrite. The resulting tan solution of iodine was immediately mixed with the alkaline P.V.P. solution, whereupon the color was instantly discharged. The solution was then dialyzed against running tap-water for forty-eight to seventy-two hours, at which time there was no longer any dialyzable radioactivity within the cellophane membrane.

Alternative methods for tagging P.V.P. with I^{131} consisted of: shaking of an aqueous solution of P.V.P. with a chloroform or carbon tetrachloride solution of I^{131}, separation of the aqueous and organic solvent layers by centrifugation, and dialysis of the aqueous phase as described above[20]; or reaction of P.V.P. with radioactive iodine monochloride.[21] The percentage incorporation of I^{131} into P.V.P. was estimated by simultaneous comparison of the counting rate of the dialyzed solution with that of an aliquot of the solution taken just prior to dialysis.

*From the Yamins and Kirstein Laboratories for Surgical Research, Beth Israel Hospital, and the Department of Surgery, Harvard Medical School.

Supported by a contract with the Office of the Surgeon General, United States Army, through the Subcommittee on Shock of the National Research Council.

†Research fellow, National Cancer Institute; research fellow, Beth Israel Hospital.

‡Assistant professor of surgery, Harvard Medical School; associate director, Surgical Research Laboratory, assistant visiting surgeon and chief, Tumor Clinic, Beth Israel Hospital.

§Professor of surgery, Harvard Medical School; surgeon-in-chief, Beth Israel Hospital.

¶Patents for the synthesis of polyvinyl pyrrolidone were filed in Germany in 1938, and pharmacologic studies on its plasma-expander properties and toxicity were begun in 1940 by Drs. Hecht and Weese,[1] of the Bayer Company, Elberfeld, Germany. Large-scale clinical application began late in 1940.

The number of atoms of iodine incorporated per molecule of P.V.P. was calculated from the data on percentage introduction of radioactivity and the estimated average molecular weight of the P.V.P. batch tagged. In 10 experiments with each of the above methods, and varying the ratio (in milligrams) of P.V.P. to iodine from 1400:1 to 70:1, between 0.6 and 1.4 atoms of iodine were introduced per molecule of P.V.P. This is consistent with addition of iodine to a single terminal double bond in each molecule of P.V.P. The most effective incorporation of I^{131} was 20 per cent of the initial radioactivity. This occurred with a P.V.P.-iodine ratio of 700:1.

C^{14}-tagged P.V.P. was provided from two sources*† for use in long-term studies on the distribution and excretion of P.V.P. in animal experiments and in clinical subjects. Since the material was prepared from radioactive acetylene, only the carbon atoms of the polyvinyl chain were thus labeled.

Fractionation for analysis of the molecular-weight spectrum of P.V.P.† was carried out either by precipitation from methanol with dry ether or from aqueous solution with acetone. There were minor differences in the molecular-weight distribution estimated by each of these methods. The I^{131}-tagged fractions were prepared by both methods. The C^{14}-P.V.P. fractions employed in tissue distribution studies were prepared in the acetone-water system.‡

Estimates of average molecular weight of whole or fractionated P.V.P. samples were made from viscosity measurements. The Fikentscher "K" value, or viscosity coefficient, was derived from the relative viscosity of 1 per cent solution of P.V.P. compared to distilled water at 20°C. according to the following formula:

$$\frac{\log u\ rel.}{c} = \frac{75K^2}{1 + 1.5\ Kc} + K$$

where u rel = relative viscosity

c = concentration of P.V.P. in gm. per 100 cc.

The average molecular weight was then calculated from the viscosity coefficient (K) by the following relation[22]:

$$2.303\ (0.001\ K + 0.000075\ K^2) = 0.0016\ M^{0.9}$$

where M is average molecular weight.

All specimens were prepared for radioactivity measurements by evaporation of an aliquot in aluminum cups coated with a thin layer of rubber cement to prevent fragmentation, distortion or loss of specimen. Whole blood, plasma, lymph, urine and bile were sampled by volume. Fresh tissue specimens were weighed wet, homogenized in water and made up to concentrations of approximately 10 to 20 mg. per cubic centimeter; 1-cc. aliquots were then evaporated in each cup. All specimens were prepared in duplicate and dried at 36°C. in a forced-draft oven. Self-absorption correction factors were determined and applied in analyses for C^{14}, but were not required for I^{131} measurements.

Expired air samples were bubbled through saturated barium hydroxide solutions to collect $C^{14}O_2$. The barium carbonate precipitate was washed several times with absolute alcohol and dried to constant weight. Measured aliquots were treated with acid in a closed system for determination of the specific radioactivity of $C^{14}O_2$ in the gas phase.

Measurements of I^{131} were made on a Tracerlab Autoscaler with a TCG-3 tube (bell-type, mica end-window weighing 1.9 mg. per square meter). The tube and samples were shielded with 3 cm. of lead. All specimens were at least five times background, and counting was continued until the probable error was reduced to 1 per cent or less. C^{14} measurements were made on a windowless proportional flow counter of the Robinson design.[23]§ Expired $C^{14}O_2$ was measured in the gas phase in a vibrating-reed, proportional-scaler counting system.¶

Procedure

In the studies on dogs, light Nembutal anesthesia was induced, a slow intravenous infusion of 0.85 per cent of sodium chloride solution started, and an indwelling catheter placed in the bladder. A rapid infusion of I^{131}-P.V.P. (50,000 to 500,000 counts per minute) was then injected through the tubing of the infusion set. Samples of venous blood were drawn into heparinized tubes at five, fifteen and thirty minutes, and one, three, six and twelve hours after the P.V.P. injection. The blood was centrifuged, and the plasma removed and plated for counting. Urine specimens were taken at three, six and twelve hours, the volume of each sample recorded, and aliquots taken for counting.

Infusions of C^{14}-P.V.P. in the rat, rabbit and dog were also rapid, but infusions in clinical patients were prolonged for forty to forty-five minutes to avoid excessively rapid expansion of the circulating blood volume. Blood and urine specimens were obtained in man at approximately the same intervals as in the experiments on dogs, the start of the infusion being taken as the zero point.

Lymph fistulas were prepared in dogs by the insertion of a polyethylene catheter into the thoracic duct via a transthoracic incision, at a point approximately 3 cm. above the diaphragm.[24]

Results

Rate of Disappearance of P.V.P. from the Blood

After the rapid infusion of I^{131}-P.V.P. in dogs, the plasma-level of radioactivity declines rapidly

*Schenley Laboratories, Lawrenceburg, Indiana.

†Central Research Laboratories, General Aniline and Film Corporation, Easton, Pennsylvania.

‡Courtesy of Dr. Kurt Ladenburg, Schenley Laboratories, Lawrenceburg, Indiana.

§Courtesy of Dr. A. K. Solomon and the staff of the Biophysical Laboratories, Harvard Medical School, to whom we are indebted for advice and guidance in the C^{14} studies.

¶Courtesy of Professor Robley Evans, Department of Physics and Radiation Laboratory, Massachusetts Institute of Technology, and Dr. Donald D. VanSlyke, Brookhaven National Laboratory, Upton, Long Island, New York.

during the first hour or two. Then follows a short "inflection phase," during which the rate of disappearance of P.V.P. from the plasma is changing rapidly. Finally, the disappearance curve approaches a straight-line decay curve with a shallow slope (Fig. 1). In all preparations studied in this manner, the inflection phase occurred at approximately the same time after the start of the infusion. The amount of P.V.P. remaining in the circulation at any one time during the initial postinfusion period, expressed in terms of percentage of administered dose, could be correlated with the K-value, or with the average molecular weight of the preparation (Fig. 1).

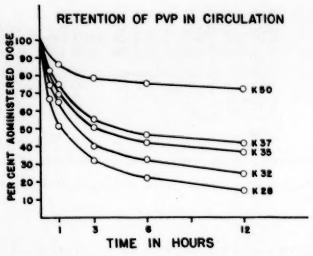


FIGURE 1. *Retention of P.V.P. in the Circulation as a Function of Molecular Size.*

The radioactivity remaining in the plasma after rapid infusion of 300 mg. of I^{131}-P.V.P. (in 10 cc. containing from 50,000 to 500,000 counts per minute) in normovolemic dogs is plotted in terms of percentage of administered dose. The concentration of I^{131}-P.V.P. in counts per minute per cubic centimeter five minutes after the infusion is taken as 100 per cent at zero time to permit dilution and nearly homogeneous distribution within the plasma volume. No correction is made for changes in plasma volume during the course of the experiment, but these are assumed to be minimal because a slow intravenous infusion of physiologic saline solution is maintained at a rate calculated to replace insensible water loss and urine formation.

Rate of Excretion in the Urine

I^{131}-P.V.P. appears in the urine soon after its infusion into the blood stream, 40 to 80 per cent of the injected dose being recovered within forty-eight hours. A small additional quantity is excreted in the third twenty-four hours. The percentage excreted is inversely correlative to the increasing K-value of the infused preparation (Fig. 2).

The percentage of the administered dose excreted during the first three or four days is constant up to a dosage level of 3.5 gm. per kilogram of body weight (equivalent to 7 liters of clinical P.V.P. in a man weighing 70 kg.). Provided that a minimum urine flow of 800 to 1000 cc. per day is maintained, the percentage excreted is also independent of the rate of urine formation.

Three hours after infusion, the amount of P.V.P. in the plasma, in addition to that excreted in the urine, is significantly less than the amount administered. For chemically fractionated specimens of low molecular weight the fraction unaccounted for reaches a peak in the next three hours and then declines gradually; for unfractionated preparations of intermediate average molecular weight the fraction reaches a maximum much later.

To determine whether the fraction unaccounted for is excreted through other portals and to what degree, if any, it undergoes metabolic degradation, a C^{14}-labeled preparation (G.A.F. No. 2809-103 K-33) was infused into man, dog and rat. The blood-disappearance and urinary-excretion curves of this preparation were similar to those obtained with radioactive-iodine-tagged P.V.P. Approximately 0.3 to 0.5 per cent of the administered dose appeared in the stool in both man and dog within twenty-four hours of infusion. Thereafter, fecal excretion fell to an average of 0.01 per cent a day. In the dog fecal excretion is entirely of biliary origin since it equals the amount of C^{14}-P.V.P. recovered in bile totally diverted through a tube in the common bile duct. Furthermore, diversion of all the bile from the intestine completely eliminated the appearance of radioactivity in the stool.

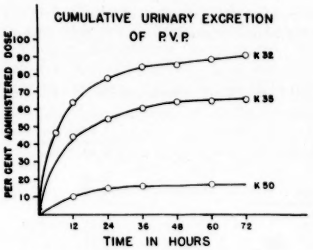


FIGURE 2. *Cumulative Urinary Excretion of P.V.P. as a Function of Molecular Size.*

The total radioactivity accumulated in successive urine specimens is plotted in terms of percentage of the administered dose. These data are obtained on the same animals used for the results described in Figure 1. Each curve represents the average values for three experiments.

Metabolism of P.V.P.

The amount of radioactive carbon dioxide in the expired air after the infusion of the same C^{14}-P.V.P. preparation (No. 2809-103, K-33) was studied to measure the extent of metabolic degradation. Between 0.15 and 0.20 per cent of the administered radioactivity (87 microcuries) was found in the expired air during the first twelve hours after infusion in man (three experiments). In subsequent twelve-

hour periods the figure fell to 0.01 per cent. After thirty-six hours no radioactivity could be detected in the expired air, even by methods sensitive to an excretion rate of 0.001 per cent a day. Since this preparation of C^{14}-P.V.P., after dialysis against running tap water for forty-eight hours prior to use, did not cause any detectable radioactivity in the expired air, the amount produced by the undialyzed material was due to a radioactive impurity of low molecular weight. It may be concluded that there is no metabolic degradation of P.V.P. and no significant route of excretion except the kidney. Consequently, the fraction not present in the blood or excreted in the urine is present in the tissues.

Distribution in the Tissues

To determine the tissue distribution of retained P.V.P. 350 mg. of C^{14}-P.V.P. (No. 2809-103, K-33) was injected intravenously into each of 6 rats, which were killed in pairs at two, four and seven weeks after infusion. The distribution of retained radioactivity in various tissues is recorded in Table 1 in counts per minute per milligram of tissue, in terms of percentage of administered dose, and in percentage of the total extravascular amount retained. A similar experiment was performed in rabbits given 8 to 9 gm. of the same preparation in seven daily divided doses, and killed at intervals of one, two and six months after infusion (Table 2). Five moribund patients received the same preparation of P.V.P. The data in a patient with adenocarcinoma of the sigmoid and liver metastases who died two months after receiving 17.5 gm. are presented in Table 3.

The distribution of retained C^{14}-P.V.P. follows a similar pattern in all three species (Tables 1, 2 and 3). The largest fraction is found in skeletal muscle and in skin and subcutaneous tissues. This is presumably due to the large size of these two organ systems (skeletal muscle is assumed to be approximately 40 per cent, and skin and subcutaneous tissues 12.5 per cent of body weight). The weight

TABLE 1. *Distribution of P.V.P. (No. 2809–103, K–33) in Organs of the Rat after Intravenous Infusion.*

ORGAN	2 WK. AFTER INFUSION			4 WK. AFTER INFUSION			7 WK. AFTER INFUSION		
	COUNT/MIN.*	AMOUNT ADMINISTERED†	AMOUNT RETAINED	COUNT/MIN.*	AMOUNT ADMINISTERED†	AMOUNT RETAINED	COUNT/MIN.*	AMOUNT ADMINISTERED†	AMOUNT RETAINED
	×10⁻³	%	%	×10⁻³	%	%	×10⁻³	%	%
Spleen	26.35	1.37	2.33	31.45	1.26	2.61	12.55	1.23	6.07
Liver	17.30	10.55	17.90	16.00	9.88	20.40	3.58	2.32	11.28
Pancreas	7.67	0.27	0.46	7.62	0.23	0.475	2.95	0.089	0.43
Skin and subcutaneous tissue	7.45	10.30	17.50	4.85	5.85	12.15	3.99	5.15	25.00
Lung	7.63	0.83	1.41	5.11	0.36	0.745	3.59	0.431	2.10
Ovary	7.30	0.045	0.076	5.92	0.02	0.041			
Muscle	3.99	17.40	29.60	3.98	14.85	30.70	1.43	5.23	25.40
Kidney	3.61	0.315	0.535	3.99	0.31	0.64	2.33	0.276	1.34
Small intestine	2.88	0.73	1.24	3.09	0.75	1.55	2.61	0.589	2.86
Heart	3.23	0.175	0.297	2.65	0.135	0.278	2.75	0.149	0.725
Residual carcass (estimated)	3.99	15.93	27.05	3.98	14.83	30.60	1.43	4.21	20.47
Totals		57.92			48.47			19.67	

*The relative concentration of P.V.P. in the tissues is expressed in terms of the radioactivity of the tissue in counts per minute per milligram of wet tissue.

†Percentage fraction of administered dose retained in each organ. Skeletal muscle mass is assumed to be 40 per cent of body weight. Skin and subcutaneous tissue is assumed to be 12.5 per cent of body weight.

TABLE 2. *Distribution of P.V.P. (No. 2809–103, K–33) in Organs of the Rabbit after Intravenous Infusion.*

ORGAN	1 MO. AFTER INFUSION			2 MO. AFTER INFUSION			6 MO. AFTER INFUSION		
	COUNT/MIN.*	AMOUNT ADMINISTERED	AMOUNT RETAINED	COUNT/MIN.*	AMOUNT ADMINISTERED	AMOUNT RETAINED	COUNT/MIN.*	AMOUNT ADMINISTERED	AMOUNT RETAINED
	×10⁻³	%	%	×10⁻³	%	%	×10⁻³	%	%
Spleen	54.40	0.324	1.26	71.20	0.144	0.59	35.00	0.192	2.36
Bone marrow				34.80	1.66	6.77			
Adrenal gland				30.60	0.03	0.12			
Liver	14.65	4.60	17.3	10.30	3.24	13.20	10.50	3.25	40.10
Testis	9.95	0.097	0.38	9.70	0.25	1.02	6.90	0.100	0.12
Skin	9.05	9.15	35.7	10.09	10.80	44.00	2.88	2.92	36.10
Kidney	8.58	0.409	1.59	5.20	0.25	1.02	6.34	0.310	3.83
Thymus	7.17	0.077	0.38	4.84	0.05	0.22			
Lung	6.53	0.284	1.10	6.65	0.19	0.77	2.78	0.075	0.92
Heart	4.43	0.084	0.33	5.00	0.10	0.41	3.14	0.054	0.67
Muscle	1.68	5.44	21.20	1.07	3.64	14.80	0.18	0.584	7.20
Stomach				1.05	0.056	0.23			
Pancreas				2.92	0.004	0.02			
Small intestine				4.83	0.550	2.24			
Thyroid gland				3.60	0.002	0.01			
Residual carcass	1.68	4.90	19.10	1.07	3.58	14.60	0.18	0.616	7.60
Totals		25.39			24.55			8.10	

*Per milligram of wet tissue.

of the "residual carcass" (bone, brain, hair and fat) was obtained by subtraction from the weight of the total carcass the combined weight of all weighed organs and tissues.

Comparison of the relative concentrations of P.V.P. in the various tissues shows that skeletal muscle and skin and subcutaneous tissue have the lowest concentration, whereas the organs of the reticuloendothelial system (liver, spleen, bone marrow and lymph nodes) have the highest. Because the major components of the "residual carcass" — that is, brain, hair and fat — showed a concentration close to that of skeletal muscle, the residual carcass was estimated to have a concentration roughly equal to that of skeletal muscle.

TABLE 3. *Distribution of P.V.P. (No. 2809-103, K-33) in Organs of Man Two Months after Intravenous Infusion.*

ORGAN	COUNT/MIN.*	AMOUNT ADMINISTERED	AMOUNT RETAINED
	$\times 10^{-4}$	%	%
Adrenal gland	9.15	0.15	0.50
Spleen	5.63	1.24	4.09
Liver	3.18	4.14	13.66
Lymph nodes	2.05	0.82	2.71
Bone marrow	1.97	1.97	6.50
Small intestine	1.00	0.80	2.64
Heart	0.93	0.32	1.06
Pancreas	0.88	0.07	0.23
Lung	0.73	0.97	3.20
Kidney	0.73	0.26	0.86
Skin	0.78	5.35	17.66
Thyroid gland	0.43	0.01	0.03
Muscle	0.35	7.65	25.25
Prostate	0.16	0.005	0.02
Residual carcass	0.35	6.56	21.65
Total		30.31	

*Per milligram of wet tissue.

Comparison of the patterns of distribution of P.V.P. at different intervals after infusion (Tables 1 and 2) reveals that the amount and concentration retained in the skin and subcutaneous tissues and in skeletal muscle decrease progressively. On the other hand the amount and concentration of P.V.P. retained in the organs of the reticuloendothelial system remain relatively constant, or at most decrease gradually during the same period of observation.

The data demonstrate first that phagocytosis of retained P.V.P. by the reticuloendothelial system appears to be largely completed within two weeks or less of its administration; secondly, that the net turnover of P.V.P. sequestered within the reticuloendothelial system is slow; and, thirdly, that the extracellular space is the major source of the slowly excreted P.V.P. that appears in the urine for as long as a year after its intravenous infusion.

The relation of the degree and pattern of retention to molecular weight was studied as follows: C^{14}-tagged P.V.P. (SL-100, K-30.2) of high specific activity (87 microcuries per gram) was fractionated into cuts of high and low molecular weight (K-37 and K-27, respectively). Three series of rats were prepared by intravenous infusion of a small dose (35 mg.) of either fraction or of the original unfractionated preparation. Paired animals from each group were killed after two weeks.

The data on residual radioactivity are presented in Table 4. The over-all retention of C^{14}-P.V.P.

TABLE 4. *Effect of Molecular Size of P.V.P. on Its Distribution and Retention in Tissues.**

ORGAN	FRACTION K-26.1		FRACTION K-30.2		FRACTION K-36.9	
	DOSE	RATIO	DOSE	RATIO	DOSE	RATIO
	%		%		%	
Spleen	0.26	1.0	1.76	6.80	3.64	14.50
Skin	7.94	1.0	18.36	2.32	24.35	3.10
Liver	1.92	1.0	5.60	2.92	6.20	3.20
Testis	0.23	1.0	0.98	4.24	1.26	5.50
Lung	0.14†		1.11		1.26	
Kidney	0.12†		0.61		0.44	
Heart	0.01†		0.29		0.34	
Muscle	5.27	1.0	14.20	2.68	19.30	3.66
Total‡	20.91	1.0	56.61	2.71	75.30	3.60

*The figures given for percentage of dose retained are average values for paired animals in each group (K-26.1, K-30.2 and K-36.9) obtained two weeks after intravenous injection of 1.0 cc. of P.V.P. The amount retained in any one organ after injection of the lowest fraction is taken as the base-line (ratio 1.0) for comparison of the effect of increasing K-value on retention of P.V.P. by each organ.

†The concentration of radioactivity in these organs was at the lower limit of sensitivity of the detection method used, and was subject to too great a probable error to provide a valid basis for comparison.

‡Including residual carcass.

increases with increasing K-value as the previous data on excretion of I^{131}-P.V.P. suggested. The most significant observation, however, is that retention of P.V.P. in the spleen (here considered as representative of the widely dispersed reticuloendothelial system) increases with increasing K-value out of proportion to that of other organs. It is noteworthy that the concentration of P.V.P. in the spleen is similar to that in other organs with the low-molecular fraction (K-26.1).

Since this is probably due to the rapid excretion of such a fraction, it appears that phagocytosis by

TABLE 5. *Molecular-Weight Distribution of C^{14}-P.V.P. (SL-100; K-30.2).**

FRACTION NO.	FRACTIONATION A†			FRACTIONATION B†	
	K-VALUE‡	MOLECULAR WT.§	WEIGHT	K-VALUE‡	WEIGHT
			%		%
1	42	117,000	23	44.1	6.7
2	37	66,000	17	40.7	9.5
3	32	45,000	19	37.2	14.0
4	28	22,000	19	34.1	14.5
5	18	15,000	22	30.8	13.3
6				27.0	13.8
7				23.1	10.9
8				16.3	12.2

*Fractionated by Dr. Kurt Ladenburg, Schenley Laboratories, Lawrenceburg, Indiana.

†Fractionation B represents a finer analysis of the size distribution of the original preparation, since the product was divided into eight fractions instead of only five. A cumulative plot of the fractions (in percentage of total) against the K-value of each fraction, reveals that these two independent fractionation analyses are practically identical.

‡Viscosity measurement.

§Light-scattering measurement.

the reticuloendothelial system is a function of a minimal limiting molecular size. A rough estimate of the minimal molecular weight of P.V.P. required to induce a phagocytic response is provided by a comparison of the molecular-weight spectrum with the pattern of retention in the tissues. This spectrum (Table 5) for the original preparation (SL-100; K-30.2), as determined by chemical fractionation in an acetone-water system followed by viscosity and light-scattering measurements, disclosed that 23 per cent of the infused P.V.P. was a K-42 fraction with a mean molecular weight of 117,000. Since approximately 10 per cent of the unfractionated P.V.P. can be estimated to have been retained by the reticuloendothelial system, it may be concluded that this system retained molecules weighing more than 117,000.

Concentration of P.V.P. in Lymph

The shape of the blood-disappearance curve is partly explained by the early and rapid loss of P.V.P. into the urine. But the persistence of a considerable, though less rapid, urinary excretion of P.V.P. for many hours after the abrupt fall in

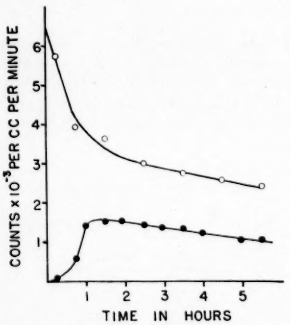


FIGURE 3. *Equilibration of I^{131}-P.V.P. between Plasma and Lymph.*

Ten cubic centimeters of I^{131}-P.V.P. (No. 124-14; K-25) was injected intravenously, and heparinized plasma and thoracic-duct lymph specimens collected at regular intervals thereafter. Open circles represent counts per cubic centimeter of plasma. Black circles represent counts per cubic centimeter of thoracic-duct lymph. (The P.V.P. was an acetone-water fraction provided by the Arnold, Hoffman Company, Providence, Rhode Island.)

the disappearance curve points to other factors. To evaluate these factors, as well as those controlling the distribution of P.V.P. within the body compartments, I^{131}-tagged fractions were administered to dogs with thoracic-duct fistulas. The equilibration of the fractions between the plasma and lymph was determined by measurement of the radioactivity in these fluids after a "rapid" injection. The results are recorded for two typical fractions in Figures 3 and 4.

These curves show that the initial rapid fall in the serum level is complementary to a rapid rise in the extracellular-fluid compartment, and that the inflection point of the blood-disappearance

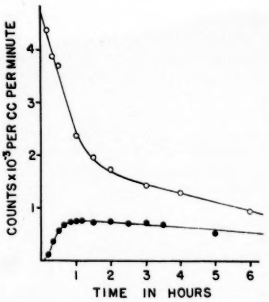


FIGURE 4. *Equilibration of I^{131}-P.V.P. between Plasma and Lymph.*

Ten cubic centimeters of I^{131}-P.V.P. (No. 2899-76; K-35) was infused, and specimens were collected as in the experiment for Figure 3. (The P.V.P. was a methanol-ether fraction provided by the General Aniline and Film Corporation, Easton, Pennsylvania.)

curve (estimated graphically as the intersection of the two limbs of the blood curve) coincides with the attainment of peak concentration of P.V.P. in the lymph. Thereafter, the concentrations of P.V.P. in the serum and lymph approach one another at a rate that is related to the K-value of the infused preparation. The rate of attainment of final equilibrium between these two compartments appears to be determined by the molecular-size distribution of the larger molecules. Thus, by extrapolation of the curves to their point of intersection, the final equilibrium of the K-25 fraction (Fig. 3) is attained in nine or ten hours, whereas that of the K-35 fraction takes more than twelve hours. Approximately 50 per cent of the K-25 fraction and 30 per cent of the K-35 fraction had left the plasma on the attainment of peak concentration in the lymph an hour after infusion. Thus, P.V.P. with a molecular weight of 20,000 or less, corresponding to the lower half of the K25 fraction, established equilibrium across the capillary barrier separating venous blood and thoracic-duct lymph within an hour.

Relation of Molecular Weight to Urinary Excretion in Man

The foregoing data demonstrate that diffusion of P.V.P. across membranes is determined primarily

by the relation between molecular size and the pore size of the membrane.

Further supporting evidence is presented in Table 6, showing that the K-value of P.V.P. extracted from the urine excreted during the first six hours after infusion of a preparation with a wide spectral range is considerably lower than that of the preparation. Since P.V.P. is not degraded, this must be due to filtration of the fractions with the lowest molecular weights. The K-value of urinary P.V.P. rises within forty-eight to ninety-six hours of

TABLE 6. *K-Value of Urinary P.V.P. in Man.*

Infused Preparation	Time of Collection		
	0-6 hr.	0-24 hr.	24-48 hr.*†
K-27	15.6	20.0	29.0
		21.0	25.7
		21.9	26.1
		22.2	28.7
		22.8	
		23.2	29.5
		24.3	
K-33	16.8		
K-42		23.8	28.4

*The K-value of P.V.P. extracted from urine by the trichloracetic acid precipitation method is corrected to an approximation of the true value by addition of 3.5 K-value units, since treatment of P.V.P. with trichloracetic acid lowers the viscosity of the polymer by this amount. The corrected values are recorded above, and may be converted to approximate mean molecular weight by the usual formula relating viscosity of P. V. P. to molecular weight.

†P.V.P. isolated from urine after twenty-four to forty-eight hours is present in such low concentrations, and so heavily contaminated with adsorbed urinary chromogens, that viscosity measurements are inaccurate. The K-value of urinary P.V.P. excreted by filtration is estimated to rise to 1 or 2 units higher than that shown for the specimens collected after twenty-four to forty-eight hours to account for the additional 2 to 5 per cent of the infused preparation that is excreted in the period from forty-eight to ninety-six hours.

administration to a peak level of K-30 or K-31, corresponding to a mean molecular weight of approximately 40,000.

The relation of the data on excretion and distribution of P.V.P. to its plasma-expanding efficiency was tested by direct measurement of plasma-volume changes induced in man. Five normovolemic subjects received 1000 cc. of 3.5 per cent K-27 P.V.P., and 5 subjects were given 1000 cc. of 3.5 per cent K-42 P.V.P. intravenously in a period of forty-five minutes. Plasma volume was measured by the radio-iodo-albumin dilution technic before infusion, at the completion of infusion and six and twelve hours after the start of the infusion. The measured increase in plasma volume and the character of the curves describing the return toward the original plasma volume was in good agreement with the values expected from studies on the disappearance rates of isotope-tagged fractions of varying molecular weight.* Thus, the initial expansion induced by 35 gm. of K-27 P.V.P. exceeded that due to 35 gm. of K-42 P.V.P., but it decreased much more rapidly.

Discussion

Our observations by radioactive-tracer technics on the fate of intravenously injected polyvinyl pyrrolidone confirm and extend the main conclusions reached in studies with less sensitive methods of analysis.[25, 26] They demonstrate that the distribution of P.V.P. among the body compartments and its manner of excretion into the urine are a process of biologic fractionation of a heterogeneous mixture of molecular sizes in the usual preparation — that is, the smaller molecules traverse the filtering membranes, and the larger molecules are retained. The dynamics of a transfer is a function of the size and shape of the polymer molecules, the size, shape and number of the pores in the membrane, the size of the membrane and the water and lipid solubility of the substance being transferred. The pore theory of capillary permeability has recently been analyzed in great detail, and the differences in pore size and filtration area of capillaries in different parts of the body have been well established.[27]

The inverse relation between the K-value of infused P.V.P. and percentage excretion in the urine and the upper limit of K-value found for urinary P.V.P. has been confirmed, with good quantitative agreement, by a number of other investigators.[28-31] That the process involved in urinary excretion is filtration is clear from the fact that the initial excretion rate in terms of percentage of administered dose of P.V.P. is the same for infusions with widely varying dosages. An analysis of the data of several investigators indicates that the maximum particle of P.V.P. filtered by the kidney has a molecular weight of 35,000 to 40,000.[22]

A similar relation has been shown between the K-value of P.V.P. and attainment of equilibrium between the plasma and extracellular fluid. The response to different fractions of a P.V.P. preparation indicates that fractions below 20,000 to 25,000 in molecular weight enter the thoracic-duct lymph from the blood stream so rapidly that they have little or no value for the expansion of plasma volume.

The absence of appreciable amounts of P.V.P. in the brain, or (in a single case) in the fetus of a pregnant rat, of animals infused with P.V.P. containing both high and low molecular sizes suggests that transfer across double barriers is far more restricted than transfer across simple capillaries.

Transfer through the glomerulus, however, is somewhere intermediate. An inverse relation between molecular size and renal clearance of macromolecules has been shown in the dog,[32] in which it is said that only 3 per cent of the glomerular capillary area is permeable to hemoglobin.[33, 34] As much as 12 per cent of the human glomerular capillary area is said to be permeable to hemoglobin (molecular weight, 68,000).[35]

The shape of the molecule, as well as its size, affects its rate of transfer. Thus, ovalbumin (molecular weight, 44,000) is reported to be as filterable through the dog's glomerulus as ovomucoid (molecular weight, 27,000). The glomerulus is less permeable to grass polysaccharide with a mean molec-

*A more detailed report of the plasma-volume expanding effect of P.V.P. and of Dextran, gelatin, plasma and saline solution in normovolemic, oligemic and shocked animals is in preparation.

ular weight of 5400 and a high fraction with a molecular weight of 9000 than to insulin (molecular weight, approximately 50,000).[38] Hence the finding of 40,000 for the upper limit of size for P.V.P. should not be surprising.

P.V.P. continues to be excreted at the rate of 25 mg. per day (0.06 per cent of a clinical dose of 17.5 gm.) for as long as twelve months. This must be from the fraction above 40,000 but less than 120,000 in molecular weight, since smaller molecules pass the glomerulus readily, whereas larger ones are retained by the reticuloendothelial system. Whether the long-term excretion of the fraction of 40,000 to 120,000 molecular weight takes place by filtration through a limited number of large pores or by a different mechanism (shedding of loaded cells) has not been determined.

The plasma-expander potential of P.V.P. is directly proportional to the amount remaining in the circulation at any one time. A given amount of material of low molecular weight exerts a greater initial expansion than an equal amount of material of high molecular weight in the same concentration, because of the greater molar concentration of the former. But this greater effect is short-lived because of its rapid excretion or transfer across capillary membranes. Almost any desired plasma-expanding effect is theoretically possible with P.V.P. by proper selection of its molecular-weight distribution and concentration. The desirable range of molecular sizes for plasma expansion is 25,000 to 40,000. A 3.5 per cent solution conforming to these specifications should induce an initial plasma-volume expansion equal to approximately 85–90 per cent of the infused volume. This would shrink to 50 to 60 per cent of the infused volume in six hours, and to 30 to 35 per cent of the infused volume in twelve hours. Approximately 60 to 70 per cent of such a preparation would be excreted within three or four days, provided a normal urine output were maintained, and the remainder would be largely eliminated within a few weeks.

Such an anticipated response in plasma expansion applies to an initially normovolemic recipient. In shock or any state of diminished circulatory volume, the expander effect would probably be enhanced by the extent of the mobilization of extracellular fluid.

An "ideal" P.V.P. preparation is difficult to manufacture at present. Existing preparations are useful, but the portion with a molecular weight below 25,000 is virtually useless, whereas that with a molecular weight well above 40,000 is retained as a foreign body. To date there is, however, no evidence that long-term retention of P.V.P. exerts any deleterious effects.

Summary

By means of radioactive-tracer technics with polyvinyl pyrrolidone (P.V.P.) fractions tagged with I^{131} and C^{14}, it has been shown that P. V. P. is not metabolized to any significant degree by the rat, dog or man. Its retention in the body is directly related to increasing molecular size. Excretion is inversely related to increasing molecular size. Its pattern of distribution in the body is also determined by molecular size. Most of it is fairly evenly distributed through the tissues. But the double-membrane barriers in brain and placenta exclude it from the brain and fetus. The reticuloendothelial system (spleen, bone marrow, lymph nodes and so forth) retains P.V.P. with a molecular weight in excess of 110,000 to 120,000 for a long time, probably years. P.V.P. with a molecular weight below 25,000 promptly leaves the glomerulus, and is therefore of no value as an effective plasma-volume expander. The glomerulus can excrete within a few days all P.V.P. of molecular weight 40,000 or below.

Since it would require extremely refined and costly fractionation procedures to produce a molecularly homogeneous preparation ideally suited for serving as a plasma-volume expander, a possible practical preparation would be one fractionated so that most of the molecules fall in the range between 25,000 and 40,000, with extreme limits of 20,000 to 70,000. An iso-oncotic, isotonic solution with these characteristics would induce an initial plasma expansion equal to about 80 to 90 per cent of infused volume. About 30 per cent of the infused volume would still act as an expander after twelve hours. Approximately 60 per cent of the preparation would be excreted into the urine within a few days, the remainder requiring a year or more to be excreted. Such a product would probably be totally excreted in time, and little if any would be stored permanently in the reticuloendothelial system.

We are indebted to Drs. Lester Persky, Stanley W. Jacob, Harold A. E. Weizel and Edward T. Gordon, Mrs. Virginia Rosenberg, Mr. David Berry and Mr. Philip Bernstein for technical assistance.

References

1. Hecht, G., and Weese, H. Periston, ein neuer Blutflüssigkeitsersatz. *München. med. Wchnschr.* **90**:11, 1943.
2. Duettmann, G. Klinische Untersuchungen und Erfahrungen mit Periston. *Deutsche Militärzt.* **9**:320-323, 1944.
3. Bourdreaux, J. Plasma sanguin conservé et plasmas artificiels synthétiques dans le traitement du shock traumatique et des hémorragies. *Paris méd.* **129**:23-28, 1945.
4. Willenegger, H., and Bruetsch, H. Klinischer Beitrag zur Wirkung des Plasmaersatzes Periston. *Helvet. chir. acta* **12**:296-307, 1945.
5. Bennhold, H., and Schubert, R. Untersuchungen über die Möglichkeit einer Vehikelfunktion des Plasmaersatzstoffes Periston. *Ztschr. f. d. ges. exper. Med.* **113**:722-736, 1944.
6. Bennhold, H., Ott, H., and Wiech, M. Über den Bindungsunterschied lebergängiger und nierengängiger Substanzen an die Serumeiweisskörper. *Deutsche med. Wchnschr.* **75**:11-15, 1950.
7. Dieckhoff, J., and Künstler, S. Zur Behandlung der alimentären Säuglingsintoxikation mit Plasma und Periston. *Monatschr. f. Kinderh.* **93**:48-68, 1943.
8. Bovet, D., Courvoisier, S., and Ducrot, R. Activité de la polyvinylpyrrolidone dans le choc traumatique expérimental et sur les accidents provoqués par certaines toxines microbiennes. *Compt. rend. Acad. sc.* **224**:70-72, 1947.
9. Schubert, R. Neu Wege der Entgiftung durch Infusion niedermolekulärer Kollidonfraktionen: vorläufige Mitteilung. *Deutsche med. Wchnschr.* **73**:551-556, 1948.
10. Muller, W. Zur pathologischen Anatomie der alimentären Intoxikation. *Deutsche med. Wchnschr.* **71**:32, 1946.
11. Schoen, H. Organveränderungen beim Säugling nach Zufuhr von Periston. *Klin. Wchnschr.* **27**:463-468, 1949.

12. Bargmann, W. Über Milzveränderungen nach Zufuhr des blutflüssigkeitsersatzes Periston. *Virchows Arch. f. path. Anat.* **314**:162-166, 1947.
13. Pellerat, J., Maral, R., and Murat, M. Histological study of viscera of guinea pigs after injection of massive doses of polyvinylpyrrolidone (Subtosan). *Rev. thérap.* **4**:No. 11, 1948.
14. Ammon, R., and Muller, W. Der Einfluss hoher Peristongaben auf den Kaninchenorganismus unter besonderer Berücksichtigung der Speicherorgane. *Deutsche med. Wchnschr.* **74**:465-468, 1949.
15. Schubert, R., and Wiegandt, E. Vorsicht bei der Beurteilung der Blutsenkungsgeschwindigkeit nach Peristoninfusionen. *Deutsche med. Wchnschr.* **70**:307-310, 1944.
16. Schubert, R. Über die Ausscheidung an Periston gebundener Stoffe (Bilirubin, Indigocarmin) und einiges über die Ausscheidung von Periston selbst. *Klin. Wchnschr.* **26**:143-149, 1948.
17. Ammon, R. Blutersatzmittel und ihr Schicksal im Organismus unter besonderer Berücksichtigung des Periston. *Med. Monatschr.* **3**: 16-22, 1949.
18. Kleiderer, I. C. *Blood Substitute, Technical Summary Report.* (P. B. Report No. 67620.) U. S. Department of Commerce, 1947.
19. Banks, H. H., Seligman, A. M., and Fine, J. Effect of hyaluronidase on absorption of parenterally administered radioactive plasma proteins in dog. *J. Clin. Investigation* **28**:548-552, 1949.
20. Fine, J., and Seligman, A. M. Traumatic shock. VII. Study of "lost plasma" in hemorrhagic, tourniquet, and burn shock by use of radioactive iodo-plasma protein. *J. Clin. Investigation* **23**:720-730, 1944.
21. Rutenburg, A. M., Seligman, A. M., and Fine, J. Studies with radioactive iodized fat. I. Preparation of radioactive fat with observations on absorption of fat following subcutaneous and intraperitoneal injection in dogs. *J. Clin. Investigation* **28**:1105-1109, 1949.
22. Warner, R. C. *Excretion of P.V.P. in Relation to Molecular Weight.* Report to National Research Council, February, 1952.
23. Robinson, C. V. Windowless, flow type, proportional counter for counting C^{14}. *Science* **112**:198, 1950.
24. Markowitz, J. *Experimental Surgery.* Second edition. 546 pp. Baltimore: Williams and Wilkins Company, 1949.
25. Loewe, H. Blutersatzmittel. *Med. Klin.* **41**:103-106, 1946.
26. Weese, H. Blutersatzmittel. *Die Pharmazie* **3**:337-340, 1948.
27. Pappenheimer, J. R., Renkin, E. M., and Borrero, L. M. Filtration, diffusion and molecular sieving through peripheral capillary membranes: contribution to pore theory of capillary permeability. *Am. J. Physiol.* **167**:13-45, 1951.
28. Welt, L. G. Progress report to National Research Council.
29. Zollinger, R. M. Progress report to National Research Council.
30. Cannan, R. K., and Welt, L. G. Progress report to National Research Council, June, 1951.
31. Cournand, A. Progress report to National Research Council, January, 1952.
32. Marshall, M. E., and Deutsch, H. F. Clearances of some proteins by dog kidney. *Am. J. Physiol.* **163**:461-467, 1950.
33. Yuile, C. L., and Clark, W. F. Myohemoglobinuria: study of renal clearance of myohemoglobin in dogs. *J. Exper. Med.* **74**:187-196, 1941.
34. Brandt, J. L., Frank, R., and Lichtman, H. C. Normal hemoglobin clearances in chronic proteinuria. *Proc. Soc. Exper. Biol. & Med.* **74**:863-865, 1950.
35. McDonald, R. K., Miller, J. H., and Roach, E. B. Human glomerular permeability and tubular recovery values for hemoglobin. *Federation Proc.* **10**:87, 1951.
36. Beattie, J., and Corcoran, A. C. Renal clearance of grass polysaccharide: observations on glomerular porosity and on relation of this function to proteinuria in renal disease. *J. Clin. Investigation* **31**: 445-450, 1952.

CHOLANGIOJEJUNOSTOMY (LONGMIRE OPERATION) FOR RELIEF OF BILIARY OBSTRUCTION DUE TO CARCINOMA*

WILLIAM R. WADDELL, M.D.,† AND CHARLES B. BURBANK, M.D.‡

BOSTON

IN 1948 Longmire and Sanford[1] described the technic of intrahepatic cholangiojejunostomy for relief of biliary-tract obstruction due to extensive destruction of the extrahepatic ducts. Since then they have reported 3 additional cases in which the procedure was successfully carried out,[2] and the reports of others have brought the total number of cases in which the operation was performed up to 8.[3-6] There have undoubtedly been other cases that have not been reported. The circumstances that warrant the operation rarely arise. Allen,[7] Cattell,[8] Lahey,[9] Cole et al.,[10] and Walters and his associates[11] have shown that biliary drainage into the intestine can be satisfactorily accomplished by other methods in a majority of cases. Nevertheless, in an occasional case intrahepatic cholangiojejunostomy is indicated, and as more experience accumulates the procedure may be more widely applicable than is believed at present. To date, no report has appeared of the use of this operation for palliation of inoperable carcinoma obstructing the bile ducts at the hilus of the liver. Because of this and to make available information from the operative result, hepatic-function studies and final autopsy specimen, a case is presented in detail.

*From the Surgical Services, Massachusetts General Hospital.

†Instructor in surgery, Harvard Medical School; assistant in surgery, Massachusetts General Hospital.

‡Assistant in surgery, Harvard Medical School; assistant in surgery, Massachusetts General Hospital.

CASE REPORT

A. W. (M. G. H. 728055), a 68-year-old domestic worker, was in excellent health until 1 month before admission to the hospital. At that time she became jaundiced; the stools became acholic, and the urine dark. Two weeks prior to admission generalized pruritus developed. No pain was experienced. Mild diarrhea and an episode of nausea and vomiting were the only other indications of gastrointestinal dysfunction.

Physical examination disclosed only deep icterus, multiple excoriations of the skin, moderate obesity and mild systolic hypertension. Laboratory data pertinent to hepatic function are summarized in Table 1. The urinary urobilinogen was 0.4 Ehrlich units, and the stool urobilinogen was negligible. Hematologic examinations, routine urinalysis, and an electrocardiogram were normal, as were roentgenograms of the chest. The feces were consistently guaiac positive. Roentgenographic examination of the upper gastrointestinal tract showed slight narrowing of the duodenum just distal to the cap but no other abnormality.

A diagnosis of extrahepatic biliary obstruction was made. Carcinoma of the pancreas or ampulla of Vater was considered the most likely cause of the obstruction. Laparotomy was performed on February 14, 1951, under nitrous oxide oxygen and ether anesthesia. A transverse incision was made. A rounded, fist-sized tumor protruded from the undersurface of the liver in the region of the gall bladder, invading the porta hepatis and the gastrohepatic ligament. The exact origin of the tumor could not be established. It appeared to extend deeply into the liver. Only the outer portion of the mass was accessible for inspection. The pylorus and duodenum were drawn up in the tumor mass. There was no possibility of resecting the tumor or of instituting biliary drainage through this area. Therefore, it was elected to establish a cholangiojejunostomy in an attempt at palliation. This was accomplished by freeing and then transecting the left lobe of the liver 2.5 cm. from its free border. Two bile ducts approximately 5 mm. in diameter were exposed. A loop of jejunum was sutured to the posterior cut edge of the liver, and a direct anastomosis between the two transected bile ducts and the mucosa of the jejunum was carried out over two 2-cm. segments of polyethylene tubing 2 mm. in diameter. Fine-silk sutures were used for these anastomoses. The tubes were used

as splints, each being held in place by a single silk suture. The serosa of the incised antimesenteric border of the jejunum was then sutured to the capsule of the cut liver anteriorly. A jejunojejunostomy was made approximately 15 cm. below the attachment of the jejunum to the liver. Two Penrose drains were inserted beneath the anastomosis and brought out through the wound. Biopsy of the tumor mass showed an undifferentiated adenocarcinoma consistent with either bile-duct or gall-bladder origin.

The postoperative course was uneventful. The highest temperature was 100.2°F. The stools were brown 4 days after operation and remained so until 8 months later. The serum bilirubin had fallen from a preoperative level of 23.0 to 6.0 mg. per 100 cc. 12 days later.

After discharge from the hospital the jaundice continued to clear, and the patient improved until readmission 7 weeks later during her first bout of cholangitis. This subsided promptly on administration of penicillin and streptomycin. Jaundice cleared completely in 3 months, but she had occasional brief bouts of cholangitis. She returned to work. Four months after operation 4300 r of x-ray therapy (tumor dose) were administered to the readily palpable right subcostal tumor mass, without discernible effect.

A gastroenterostomy was performed 6½ months after the original operation, to relieve duodenal obstruction caused by the enlarging tumor. Peritoneal implants of tumor were observed. The patient was mildly icteric (Table 1), but continued to have bile in her stools until 2 months later. Despite gradually increasing jaundice she was able to resume work for a while, but over the next 4 months her condition deteriorated, and she died 13 months after the establishment of the diagnosis and first operation.

FIGURE 1. *Transverse Section through the Middle Portion of the Liver Viewed from above.*
On the right is the atrophied lobe, and on the left the hypertrophied left lobe, within which the dilated left hepatic duct and its major radicles can be seen, with probes passing into the jejunum. The tumor mass occupies the middle portion of the liver.

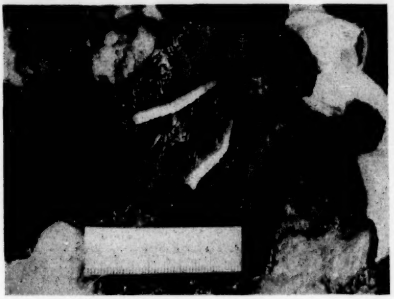


FIGURE 2. *Undersurface of the Specimen Shown in Figure 1, Demonstrating the Jejunal Attachment to the Liver and the Patent Anastomoses.*

At autopsy the tissues were deeply icteric and there was evidence of much wasting. The abdominal cavity contained several liters of ascitic fluid. There were innumerable carcinomatous implants over the peritoneal surface. The central portion of the liver was replaced by a large tumor mass, which extended directly into the porta hepatis and involved the distal end of the stomach, the duodenum, the pancreas and the retroperitoneal area of the right upper abdomen. Approximately two thirds of the mass was within the liver and so situated that the common hepatic duct and distal portions of the right and left hepatic ducts were completely replaced by tumor tissue (Fig. 1). There were a few scattered nodules of cancer in the remaining liver tissue, but for the most part the tumor had grown by direct extension. The gall bladder contained a single large stone. It was surrounded by tumor, but the mucosa was intact.

The duct system of the left lobe was widely dilated, in contrast to that on the right. The mass of liver tissue was greater in the left than in the right lobe, which was firmer. The plastic tubes over which the two radicles of the left hepatic duct had been anastomosed to the jejunum were in place, and their lumens were completely occluded by bile-salt deposits. After removal of the tubes the anastomoses were shown to be patent by ready passage of probes, although

TABLE 1. *Laboratory Data.**

DATE	CLINICAL STATUS	SERUM BILIRUBIN	SERUM ALKALINE PHOSPHATASE	PROTHROMBIN TIME	CEPHALIN FLOCCULATION	
		mg./100 cc.	*Bodansky units*	*% of normal*	*in 24 hr.*	*in 48 hr.*
2-8-51	Before operation	23.0	21.7	70	—	—
2-26-51	12 days after operation	6.0	21.1	—	—	—
3-12-51	1 mo. after operation; patient asymptomatic.	3.0	25.6	—	0	0
4-3-51	Cholangitis	3.7	30.4	—	+	++
5-14-51	Patient asymptomatic and working	0.9	—	—	++	++
8-20-51	Pyloric obstruction; patient jaundiced and dehydrated.	2.3	35.3	100	+	+
12-19-51	Jaundice and cholangitis	19.6	—	57	+++	+++
2-19-52	Terminal phase	29.4	—	—	—	—

*Summary of laboratory data pertaining to hepatic function.

the more medial of the two was partially surrounded by tumor tissue and almost surely would have been occluded except for the presence of the plastic tube. The anastomosis between the lateral duct and the jejunum was tightly constricted about the plastic tube and almost certainly would have been stenosed at this point had the tube not been in place. Figures 1 and 2 show the probes passing through the anastomoses from the hepatic and jejunal sides respectively.

Microscopical examination showed the tumor to be a Grade 4 adenocarcinoma consistent with bile-duct origin. The liver tissue of the left lobe was involved in an extensive and severe inflammatory process arising from a purulent cholangitis. The right lobe was not grossly involved in this infection. The hepatic tissue demonstrated advanced biliary cirrhosis in the right lobe, the biliary drainage of which had been obstructed for at least 14 months. There was a similar but less severe cirrhotic process involving the left lobe.

Discussion

It is quite obvious that circumstances rarely warrant the use of this operation as a palliative procedure. Only an occasional carcinoma of the gall bladder, hepatic-duct system, pancreas, kidney, colon or stomach will be so situated as to obstruct biliary drainage at the porta hepatis and prevent establishment of internal drainage through that area. If the patient's general condition is such as to indicate survival for a reasonable length of time, relief of itching, clearance of icterus and improved digestion may constitute real palliation. Perhaps more important is the relief of the anguish that must accompany the patient's realization that operation was unsuccessful. In the case reported above, the patient's life was unquestionably extended and made easier for at least eight months, perhaps longer and during that period she was able to work. Neibling et al.,[12] at the Mayo Clinic, found an average survival of only three or four months after operation for bile-duct carcinomas.

Technically, the operation is not difficult or unduly strenuous for the patient. The major blood supply accompanies the larger biliary radicles, and the vessels can be secured individually. Oozing from the cut surface of the liver can be controlled manually or with an intestinal clamp shod with shoelace instead of rubber, to prevent its slipping off during placement of mattress sutures.

Several technical changes could have made our efforts more successful. In the first place, a gastroenterostomy at the time of the first operation would have eliminated the second operation for relief of pyloric obstruction. This was considered, but it was decided that the patient probably would not survive long enough for obstruction to develop at that point. A Roux Y rather than a loop of jejunum might have lessened or eliminated the occasional bouts of cholangitis. The performance of the anastomoses of the two dilated biliary radicles to the jejunal mucosa over polyethylene tubes ultimately resulted in defeat of the aims of the operation. It had been thought that these smooth tubes, each held in place by a single silk stitch, would later pass on into the intestine. They remained, however, and eventually both became occluded by deposition of bile salts. This complication has often followed the placement of permanent prostheses within the common bile duct.[13, 14] Nevertheless, as in the reconstructed common bile duct, a long period of intubation appears necessary to prevent the contraction of circular scar tissue. Lahey[9] has recommended that a T-tube be left in place for a year after reconstruction of the common bile duct, and this coincides with the experience in this hospital.[15-17] With this background it is suggested that when cholangiojejunostomy is performed enough of the duct be exposed to allow placement of a small T-tube with one arm passing through the anastomosis, and that this be left in place for many months, to be cared for in the usual manner with daily irrigations and early removal only if it becomes occluded. This precaution should minimize late strictures and repeated bouts of cholangitis, and perhaps extend the usefulness of the operation.

The functional capacity of the left lobe of the liver has been subject to question, but it appears from this case and others in which only the left

Table 1 (*Concluded*).

Date	Thymol Turbidity	Flocculation	Serum Total Protein	Serum Albumin	Serum Globulin	Albumin-Globulin Ratio	Total Cholesterol	Cholesterol Esters
	units/100 cc.		*gm./100 cc.*	*gm./100 cc.*	*gm./100 cc.*		*mg./100 cc.*	*mg./100 cc.*
2-8-51	3.5	0	6.99	4.04	2.95	1.4	—	—
2-26-51	—	—	—	—	—	—	—	—
3-12-51	—	—	6.28	3.68	2.60	1.4	302	168
4-3-51	2.0	0	6.87	3.98	2.89	1.4	—	—
5-14-51	—	—	6.70	3.32	3.38	1.0	206	90
8-20-51	—	—	7.26	3.93	3.63	1.1	266	147
12-19-51	—	—	7.50	—	—	—	—	—
2-19-52	—	—	—	—	—	—	—	—

hepatic duct was drained, that the left lobe alone is entirely adequate,[6, 18] even when a portion of it has been resected. This is consistent with the behavior of hepatic tissue in animals, in which excision of large portions of the liver results in rapid regeneration of the remaining tissue.[19, 20] The size of the left lobe of the patient's liver indicates that such a regeneration had occurred. The regression of the right lobe apparently resulted from long-standing obstruction, cirrhosis, parenchymal atrophy and scarring. The fact that the right biliary radicles were not dilated indicates long-standing obstruction and cessation of secretory activity, and probably constitutes valid evidence of the origin of the tumor within the intrahepatic duct system.

The laboratory data pertinent to hepatic function are recorded in Table 1. The complete clearance of jaundice was substantiated chemically. The persistent elevation of the alkaline phosphatase probably resulted from continued obstruction of the right hepatic duct and is a further indication that only the left lobe was drained.[21-23] Synthetic functions of the liver, as determined by total protein, serum albumin and globulin, cholesterol and cholesterol esters and prothrombin levels, all remained normal. The cephalin flocculation did not become seriously altered until biliary drainage ceased and the patient was deteriorating.

Summary

A case in which cholangiojejunostomy was carried out as a palliative procedure is described. Biliary-tract obstruction resulting from carcinoma arising in the bile ducts was relieved for eight months, and the patient survived for thirteen months. The left lobe of the liver, a portion of which was resected, proved adequate for maintenance of various synthetic functions. On the basis of experience with this case several suggestions for palliation are made.

We are indebted to Dr. Norman Zamcheck, Mallory Institute of Pathology, Boston, who performed the autopsy.

References

1. Longmire, W. P., Jr., and Sanford, M. C. Intrahepatic cholangiojejunostomy with partial hepatectomy for biliary obstruction. *Surgery* **24**:264-276, 1948.
2. *Idem.* Intrahepatic cholangiojejunostomy for biliary obstruction — further studies: report of 4 cases. *Ann. Surg.* **130**:455-465, 1949.
3. Sanders, R. L. Hemihepatectomy with hepaticojejunostomy for irreparable defects of bile ducts. *Arch. Surg.* **58**:752-761, 1949.
4. Wilson, H., and Gillespie, C. E. Partial hepatectomy with intrahepatic cholangiojejunostomy: useful addition to technical methods for management of common duct stricture. *Ann. Surg.* **129**:756-765, 1949.
5. Massie, F. M. Longmire operation for common duct obstruction. *Ann. Surg.* **131**:838-845, 1950.
6. Cole, W. Discussion of Longmire and Sanford.[3]
7. Allen, A. W. Method of re-establishing continuity between bile ducts and gastro-intestinal tract. *Ann. Surg.* **121**:412-424, 1945.
8. Cattell, R. B. Benign strictures of biliary ducts. *J. A. M. A.* **134**: 235-240, 1947.
9. Lahey, F. H. Further experiences with injured bile ducts: new method of repair. *New Eng. J. Med.* **240**:161-168, 1949.
10. Cole, W. H., Reynolds, J. T., and Ireneus, C., Jr. Strictures of common duct. *Ann. Surg.* **128**:332-347, 1948.
11. Walters, W., and Phillips, S. K. Increasing frequency of injury to common bile duct and hepatic duct. *Surgery* **25**:469-471, 1949.
12. Neibling, H. A., Docherty, M. B., and Waugh, J. M. Carcinoma of extrahepatic bile ducts. *Surg., Gynec. & Obst.* **89**:429-438, 1949.
13. Pearse, H. E. Results from using vitallium tube in biliary surgery. *Ann. Surg.* **124**:1020-1029, 1946.
14. Walters, W. Physiologic studies in cases of stricture of common bile duct. *Ann. Surg.* **130**:448-454, 1949.
15. Allen, A. W. Personal communication.
16. McKittrick, L. S. Personal communication.
17. Bartlett, M. K. Personal communication.
18. Cattell, R. B. Discussion of Longmire and Sanford.[3]
19. Higgins, G. M., and Anderson, R. M. Experimental pathology of liver. I. Restoration of liver of white rat following partial surgical removal. *Arch. Path.* **12**:186-202, 1931.
20. Brues, A. M., Drury, D. R., and Brues, M. C. Quantitative study of cell growth in regenerating liver. *Arch. Path.* **22**:658-673, 1936.
21. Freeman, S., Chen, Y. P., and Ivy, A. C. On cause of elevation of serum phosphatase in jaundice. *J. Biol. Chem.* **124**:79-87, 1938.
22. Schiffmann, A., and Winkelman, L. Influence of liver on serum phosphatase. *Arch. Int. Med.* **63**:919-929, 1939.
23. Gutman, A. B., Hogg, B. M., and Olson, K. B. Increased serum phosphatase activity without hyperbilirubinemia after ligation of hepatic ducts in dogs. *Proc. Soc. Exper. Biol. & Med.* **44**:613-617, 1940.

PURPURA FULMINANS*

Report of Two Cases Following Scarlet Fever

WILLIAM N. CHAMBERS, M.D.,† JOHN B. HOLYOKE, M.D.,‡ AND ROBERT F. WILSON, M.D.§

HANOVER, NEW HAMPSHIRE

PURPURA fulminans is a rare clinical syndrome characterized by sudden appearance of rapidly progressive symmetrical subcutaneous ecchymoses and accompanied by high fever, intense systemic symptoms and death, which usually occurs within a few days of the onset.

Ever since this syndrome was first described by Guelliot[1] in 1884 there have been scattered reports in the literature of cases, all characterized by strikingly similar clinical courses, hemorrhagic manifestations and autopsy findings. The laboratory investigations in most cases are equivocal. In a number of cases the fulminating purpura is preceded by scarlet fever, suddenly appearing in the second to the fourth week after the disease. It may follow other infectious diseases, but frequently there is no known predisposing cause.

Recovery from this condition is extremely rare, only 7 survivals out of approximately 100 cases being reported. Recovery in 2 cases followed amputation of the most severely involved extremity.[2, 3] Two survivals have been reported after treatment with methionine.[4]

In two extensive reviews of scarlet fever[5, 6] only 4 cases of purpura fulminans were found. It is of interest therefore that 2 patients with this condition after scarlet fever were seen at this hospital in January, 1947, and May, 1948, respectively.

CASE REPORTS

CASE 1. An 8-year-old girl had been well until scarlet fever developed, for which she was treated symptomatically by her family physician. No sulfonamides were used. The disease was not severe, and she had a normal convalescence until 19 days after the onset, when a painful ecchymotic area appeared on the left thigh and buttock. On the following day a similar area appeared on the right thigh. Both areas increased rapidly in size.

The patient was admitted to the hospital 2 days later. She was alert and co-operative, but cried frequently because of pain in the abdomen and chest. Both legs were tender and firm, and showed massive swelling and ecchymosis involving approximately 60 per cent of the skin of the lateral and posterior aspects of the thighs (Fig. 1). There was tenderness without spasm throughout the lower abdomen.

The temperature was 100°F. by rectum, the pulse 110, and the respirations 24.

The red-cell count on the morning after admission was 3,530,000, with a hemoglobin of 9.5 gm. per 100 cc., and the white-cell count was 29,750, with 78 per cent segmented neutrophils, 21 per cent lymphoyctes and 1 per cent monocytes. The platelets appeared slightly decreased in the smear, but no counts were made. Examination of the urine showed a specific gravity of 1.017 and an albumin of 0.5 gm. per 100 cc.; microscopical analysis of the centrifuged sediment demonstrated 2 white blood cells, no red blood cells and 8 hyaline casts per ten high-power fields.

Because it was believed that fresh blood would be most helpful in combating the bleeding, transfusion was delayed for 14 hours while such blood was being obtained. At that time the patient was in a state of peripheral vascular collapse.

FIGURE 1. *Extensive Ecchymoses of the Thighs in Case 1.*

Despite the administration of approximately 1000 cc. of fresh whole blood and 250 cc. of plasma, vitamin C and K and rutin, there was a rapid extension of the ecchymotic areas to involve almost all of both lower extremities and the lower abdominal wall. She had severe pain in all the involved areas but remained clear mentally until a short time before death, which occurred 27 hours after admission and only 3 days after the onset of the first symptoms of purpura. Permission for an autopsy was refused.

CASE 2. Three weeks before admission a 14-year-old schoolgirl had a sore throat, headache, vomiting and a high temperature. A diffuse erythematous rash developed on the following day. A diagnosis of scarlet fever was made and 1 gm. of sulfadiazine every 4 hours was given for 1 week. Moderate desquamation occurred from the extremities. Two weeks after the onset of the illness epistaxis, conjunctivitis and mild joint pains developed. Fever recurred and was accompanied by tachycardia. Aspirin, in a dosage of 10 gm. daily, was given. Sulfadiazine was started again. Because of the persistence of fever, crystalline penicillin, 300,000 units intramuscularly twice daily, was given for 2 days. In spite of this,

*From the Hitchcock Clinic, and the departments of Medicine and Pathology, Dartmouth Medical School.

†Instructor in medicine, Dartmouth Medical School; associate, Department of Medicine, Hitchcock Clinic; attending physician, Mary Hitchcock Memorial Hospital.

‡Assistant professor of pathology, Dartmouth Medical School; associate, Hitchcock Clinic and Mary Hitchcock Memorial Hospital.

§Formerly, resident in pediatrics, Hitchcock Clinic and Mary Hitchcock Memorial Hospital.

the temperature rose to 103°F. At that time vesicular lesions were noted on both ankles and there was slight swelling of both wrists.

On admission the patient was acutely ill. The skin was hot and dry, and the face was puffy. The tongue was denuded. The tonsils were enlarged and cryptic bilaterally and free from exudate. Tachycardia was the only abnormal cardiac finding. The lungs were clear. The spleen and liver were not palpable. The reflexes were equal and active. The lymph nodes were not enlarged.

The temperature was 104°F. by mouth, the pulse 140, and the blood pressure 120/70.

On the dorsa of both feet and extending up the lateral aspect of both legs were symmetrical areas of erythema and ecchymosis. Small splinter hemorrhages were noted on the

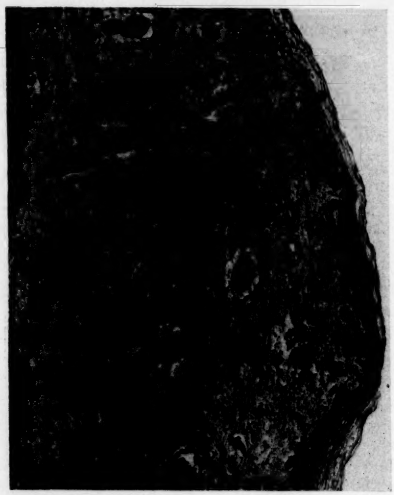


FIGURE 2. *Photomicrograph of the Skin of the Right Lower Extremity in Case 2 (Hematoxylin and Phloxine Stain X75), Showing Vascular Necrosis and Hemorrhage.*

tips of the fingers and toes. Scattered minute petechiae were present on the trunk.

Examination of the urine showed a specific gravity of 1.011. The albumin was 0.007 gm. per 100 cc. The sediment was loaded with round and squamous epithelial cells, and there were 8 white blood cells and 10 red blood cells per ten high-power fields. Examination of the blood disclosed a red-cell count of 4,100,000, with a hemoglobin of 11.7 gm. per 100 cc., and a white-cell count of 4700, with 73 per cent segmented neutrophils, 19 per cent lymphocytes and 8 per cent monocytes. The erythrocyte sedimentation rate was 73 mm. per hour. The blood Mazzini test for syphilis was negative. Repeated blood cultures were sterile. Culture of the throat revealed a mixture of organisms, largely *Streptococcus viridans*. The capillary fragility test was negative. The prothrombin time (Quick one-stage method) was 20.8 seconds, with a control of 15.8 seconds (40 per cent of mean normal in this laboratory). A repeat prothrombin time 3 days later was 21.2 seconds, with a control of 15.3 seconds (38 per cent of mean normal). The bleeding time was 13 minutes, 25 seconds (normal, 1 to 3 minutes). The clotting time was 4 minutes, 23 seconds, by the capillary tube method (normal, 3 to 7 minutes with this technic). Three days later the bleeding time was 7 minutes, and the clotting time 5 minutes. The sulfadiazine level was too low to measure. The nonprotein nitrogen was 23 mg. per 100 cc. The patient's blood group was AB and she was Rh +. Three days later the hemoglobin was 10.9 gm., and the red-cell count was 4,050,000. The total white-cell count at that time was 23,300, with 81 per cent segmented neutrophils, 6 per cent stab forms, 8 per cent lymphocytes, 4 per cent monocytes and 1 per cent metamyelocytes. The platelets, which were not counted, appeared slightly decreased in the smear. X-ray study of the chest revealed increased density in the left-lower-lung field, with thickening of the markings, indicative of partial consolidation. Two days later the bronchovascular markings on the right were increased. Fluoroscopic examination of the heart was negative. Serial electrocardiograms showed only sinus tachycardia. Sternal-marrow aspiration demonstrated slight hypoplasia of the erythroid elements.

The patient's clinical course was characterized by spiking fever, tachycardia and gradual extension of the hemorrhagic manifestations. The subcutaneous ecchymoses, which had originally consisted of localized areas on the feet and ankles, rapidly spread to involve both lower extremities. Crystalline penicillin, transfusions of whole blood and massive doses of menadione, rutin and vitamin C were given. In spite of this the patient's condition became rapidly worse. The subcutaneous ecchymoses became increasingly massive and cyanotic. On the 5th hospital day she complained of severe urinary urgency, but was unable to urinate. A catheterized specimen showed gross hematuria. An indwelling catheter was inserted. She was put in an oxygen tent. The subcutaneous ecchymoses had extended up to the hips and involved the labia, which were swollen and purple. One hour before death the blood pressure was 120/60, and the pulse was 100. The patient then became extremely anxious, and gasping respirations developed. Pallor of the face and upper extremities appeared. She lapsed into unconsciousness and died.

At autopsy the peritoneal cavity contained 1500 cc. of bloody fluid. There was hemorrhage in the soft tissue about the bladder. The broad ligaments were distended with blood. The right kidney weighed 120 and the left 125 gm. The capsules stripped with ease, revealing pale, smooth surfaces. There were hemorrhages in the tissues of the calyxes and pelves. There was blood in the wall and in the lumen of the ureters. The wall of the urinary bladder was markedly edematous and contained large quantities of extravasated blood. There was clotted blood in the uterine cavity. The endometrium was red. Each ovary measured 4 by 3 by 2 cm. and contained small, thin-walled, blood-filled cysts up to 0.8 cm. in diameter. There were an estimated 25 cc. of clotted blood in the vagina. The distal 4 cm. of the vena cava and both common iliac veins were partially occluded by a friable thrombus, which was adherent at the bifurcation of the vena cava. There were calcified flecks in the lymph nodes at the hili of the lungs. The heart, liver, spleen, pancreas, cerebral nervous system and intestinal tract were normal on gross examination.

Microscopical examination showed the sinuses of the spleen to be packed with macrophages and plasma cells. There were small areas of necrosis adjacent to the capsule. The walls of scattered arterioles and veins were necrotic. There were a few neutrophilic leukocytes in the necrotic vessel walls, but this was not a prominent feature of the vascular change. The endometrium contained extensive extravasated blood in the stroma. There were necrosis, hemorrhage and necrotic arterioles and veins in the sections of ovary. The vascular lesion was similar to that in the spleen. In the kidneys there were occasional tubules, which were necrotic and contained amorphous débris. In and about these tubules there were large numbers of monocytes and macrophages. In the lungs scattered small arteries were occluded with amorphous pink-staining material. In sections of the skin the arteries and veins were necrotic. Exudate in the necrotic segments of vessels was scanty and consisted of neutrophilic leukocytes. The superficial areas, including the epidermis and outer portions of the dermis, were necrotic. Many vessels were thrombosed. There was abundant extravasated blood in the cutis (Fig. 2). The pancreas, thymus, cerebellum, cerebrum, spinal cord, pons, heart, liver, breasts and thyroid and adrenal glands were normal. Blood cultures were sterile.

Anatomic diagnoses were as follows: necrotizing vasculitis of the ovaries, spleen, skin and subcutaneous tissues of the lower extremities; hemorrhage of the skin and subcutaneous tissues of the lower extremities, pelvic viscera, kidney pelves and ureters; thrombosis of the inferior vena cava, common iliac veins and branches of the pulmonary arteries; and old tuberculosis of lymph nodes of hili of the lungs.

Discussion

These 2 cases are similar in many respects. Each patient was young and was convalescent from relatively mild scarlet fever. The interval between onset of illness and appearance of the hemorrhagic manifestations was approximately three weeks in each case. The lesions were painful and symmetrical and involved the lower extremities. There was rapid extension of the ecchymoses in each case. Both were characterized by fever, secondary anemia, leukocytosis and probably a slight reduction in platelets. Death, which occurred six days after the first appearance of hemorrhagic manifestations, was apparently due to massive exsanguination into the subcutaneous tissues and occurred in spite of transfusions and large doses of vitamin C, vitamin K and rutin. Although the prothrombin time was abnormal in Case 2 its prolongation was not considered sufficient to explain the hemorrhagic manifestations; one estimation of the bleeding time was prolonged, but a second test was within normal limits.

The laboratory findings were equivocal and did not explain the cause of the hemorrhagic manifestations. Similar data are reported in the literature.

The post-mortem findings in Case 2 were those of a necrotizing vasculitis involving the kidneys, pelvic organs, spleen and lower extremities. Similar autopsy findings have previously been reported.[7, 8] The possible cause for these changes could have been either hypersensitivity to the sulfonamides or to hemolytic-streptococcus toxin, or hypersensitivity to an antibody. There are many articles in the literature concerning the development of hypersensitivity to sulfonamides with resultant widespread polyvasculitis of a necrotizing nature.[9-12] However, toxic purpura following scarlet fever is a well defined condition that was recognized clinically and pathologically many years before the discovery of the sulfonamides. The following statement of More et al.[12] is of interest:

> Many etiological agents are capable of producing lesions similar to those caused by the sulfonamides. While the cause of the polyvascular inflammatory lesions is unknown, this lesion is found in many diseases that may or may not be related in etiology or pathogenesis.

Various other theories have been advanced as explanations of this type of toxic purpura. In cases that develop after scarlet fever, increased capillary permeability due to the action of the scarlet-fever toxin on the blood vessel is generally accepted.[13] Sensitization of the capillary endothelium by the scarlet-fever toxin or by any other substance capable of inducing hypersensitivity in a susceptible person may be responsible for this increased permeability. In 59 autopsies on patients with scarlet fever, Brody and Smith[8] demonstrated a characteristic pathological change in the vessel walls, with a concurrent perivascular "round-cell" infiltration. They believed that these changes were due to the circulating toxin. Although there are no reports in the literature concerning the experimental production of hemorrhagic manifestations with scarlet-fever toxin, this has been done with the meningococcus. Shwartzman[14] has demonstrated a neuropurpurogenic factor in this organism. In rabbits, Black-Schaffer et al.[15] have reproduced the Waterhouse–Friderichsen syndrome, with its characteristic cutaneous purpura, by the injection of meningococci.

The possibility of liver dysfunction as an explanation for increased capillary permeability was first suggested by Rabinowitz.[16] Kaufman[4] recently reported 2 cases of post-scarlatinal purpura treated successfully with methionine. Discontinuation of methionine resulted in recrudescence of the purpura, which subsided on reinstitution of the drug.

There are no reports in the literature concerning the treatment of purpura fulminans with ACTH or cortisone. However, striking clinical improvement in 4 cases of allergic purpura of the Schönlein — Henoch type were recently reported to have followed the use of cortisone.[17]

Summary

Two cases, both characterized by fulminating subcutaneous hemorrhages involving the lower extremities, with death three weeks after scarlet fever, are reported. Laboratory findings were equivocal. Autopsy in 1 case revealed necrotizing vasculitis and thrombosis of the vena cava and iliac vessels.

References

1. Guelliot, A. Note sur trois cas de purpura infectieux foudroyant. *Union méd. et scient. du nord-est* **8**:25-37, 1884.
2. Dick, G. F., Miller, E. M., and Edmondson, H. Severe purpura with gangrene of lower extremity following scarlet fever: recovery after amputation. *Am. J. Dis. Child.* **47**:374-377, 1934.
3. Webb, B. D., Dubs, E. J., and Conrad, E. J. Postscarlatinal gangrene with prolonged prothrombin time. *J. Pediat.* **30**:76-81, 1947.
4. Kaufman, B. Methionine in control of bleeding and restoration of normal clot retraction in purpura following scarlet fever. *Arch. Pediat.* **63**:282-290, 1946.
5. Hunt, L. W. Hemorrhagic purpura in scarlet fever: report of 2 cases. *Am. J. Dis. Child.* **56**:1086-1090, 1938.
6. Fox, M. J., and Enzer, N. Consideration of phenomenon of purpura following scarlet fever. *Am. J. M. Sc.* **196**:321-329, 1938.
7. McConnell, G., and Weaver, H. L. Purpura fulminans during convalescence from scarlet fever. *J. A. M. A.* **78**: 165-168, 1922.
8. Brody, H., and Smith, L. W. Visceral pathology in scarlet fever and related streptococcus infections. *Am. J. Path.* **12**:373-394, 1936.
9. Rich, A. R. Role of hypersensitivity in pathogenesis of rheumatic fever and periarteritis nodosa. *Proc. Inst. Med. Chicago* **15**:270-280, 1945.
10. Lichtenstein, L., and Fox, L. J. Necrotizing arterial lesions resembling those of periarteritis nodosa and focal visceral necrosis following administration of sulfathiazole: report of case. *Am. J. Path.* **22**: 665-677, 1946.
11. French, A. J. Hypersensitivity in pathogenesis of histopathologic changes associated with sulfonamide chemotherapy. *Am. J. Path.* **22**:679-701, 1946.
12. More, R. H., McMillan, G. C., and Duff, G. L. Pathology of sulfonamide allergy in man. *Am. J. Path.* **22**:703-735, 1946.
13. Krache, R. R. *Diseases of the Blood.* Second edition. 712 pp. Philadelphia: Lippincott, 1941. P. 460.
14. Shwartzman, G. *Phenomenon of Local Tissue Reactivity and Its Immunological, Pathological and Clinical Significance.* 461 pp. New York: Paul B. Hoeber, 1937. P. 378.
15. Black-Schaffer, B., Hiebert, T. G., and Kerby, G. P. Experimental study of purpuric meningococcemia in reaction to Shwartzman phenomenon: with discussion of meningococcic purpura, Waterhouse-Friderichsen syndrome. *Arch. Path.* **43**:28-54, 1947.
16. Rabinowitz, H. M. Study of role of amino acids in clot retraction: effect of methionine in restoring normal clot retraction and control of bleeding in essential thrombocytopoenic purpura. *Am. J. Surg.* **51**:366-378, 1941.
17. Kugelman, I. N. Cortisone in allergic purpura of children. *New York State J. Med.* **51**:2504-2506, 1951.

MEDICAL PROGRESS

PEDIATRICS*

JAMES MARVIN BATY, M.D.,† MARSHALL B. KREIDBERG, M.D.,‡ AND ORVAR SWENSON, M.D.§

BOSTON

IN the last progress report on pediatrics, Richard M. Smith[1] outlined the growth of the specialty during the first half of this century. He mentioned many of the individuals and organizations that had made important contributions, not only to the development of this branch of medicine but particularly to the solution of the more vexing problems of infancy and childhood, as they existed at the turn of the century and as they subsequently appeared in altered form. It is obvious that at the beginning of this period the greatest hazards in infancy and childhood were presented by the problems of diet and infectious diarrhea. These problems were largely resolved during the first quarter of the century; during the second quarter, great progress was made in control of the mortality in infectious conditions. It can be stated without question that, as a result of advances in the understanding of the problems of nutrition, epidemiology and preventive medicine, and the discovery of the new chemotherapeutic drugs and antibiotics, infants and children have a greater life expectancy, enjoy greater physical vigor, attain greater physical stature and are subject to fewer ailments at present than at any other time in the history of mankind. This statement, although valid, is only a half truth. The ailments of man, as pointed out so vividly by Hans Zinsser in *Rats, Lice and History*, have all changed through gradual processes over long periods. Obviously, the problems of child care have not been solved — they are simply different.

There are still many unsolved or only partly understood problems — notably cancer, congenital malformations, and prematurity — that justly deserve the continued interest and unceasing activity of the many individuals and groups working in these particular fields. The greatest challenge facing society in general, and those interested in infants and children in particular, is the fostering of emotional and intellectual development. The constant accounts in the daily newspapers of acts of delinquency by the juvenile population indicate the scope of this problem, and the incidence of mental illness offers further confirmation. Since the pediatrician deals with the individual in his formative years, he should be concerned with development of the personality and function of the emotions as part of the total care of the patient.

Isolated individuals and groups have recognized and attempted various approaches to this problem for over twenty years. The Commonwealth Fund of New York, in particular, has done pioneer work by supporting studies in a few teaching centers to demonstrate the practicability of increasing the scope of pediatric teaching programs by a broader understanding of the emotional and psychologic problems of children. The interest in, and comprehension of, this phase of child care has spread so rapidly during the past five or six years that the majority of pediatric centers in the country include groups that have undertaken the study of the emotional and intellectual development of the child.

Experiments in pediatric education are being carried out — as yet, unfortunately, only in isolated instances — with the purpose of shifting emphasis from the study of "diseases" and "abnormalities" to the consideration of the child as a human being with feelings, intellect and individuality, who may be beset by a variety of ailments and environmental disturbances. Indications are that this trend may gradually alter the entire philosophy of medical education.[2-4] The transition will be slow in developing, however, since the present system of medical education was designed to meet problems as they existed before and during the first half of this century.

ROOMING-IN

During recent years there has been considerable discussion in the medical[5, 6] and in the lay press on problems of maternal and infant care, with special emphasis on "natural childbirth," "rooming-in" and "self-demand" feeding regimens. In a careful review and evaluation of the literature on obstetric and neonatal care, Reid and Cohen[7] pointed out that there are no scientific data to support most of the ideas and suggestions for modifications in modern obstetric management and hospital procedure. Their conclusion was that although the science of psychology is not incompatible with the science of obstetrics, the bases for modifications should be obtained by careful investigation under properly controlled conditions.

McBryde[8] has summarized a compulsory rooming-in plan involving about 2000 deliveries of ward and private patients and reported that the nursing

*From the Pediatric and Surgical Staff, Boston Floating Hospital and Tufts College Medical School.

†Professor of pediatrics, Tufts College Medical School; physician-in-chief, Boston Floating Hospital.

‡Assistant professor of pediatrics, Tufts College Medical School; physician, Boston Floating Hospital.

§Associate professor of surgery, Tufts College Medical School; surgeon-in-chief, Boston Floating Hospital.

costs of the rooming-in program were less than those of a newborn nursery, and that no special equipment or modification of rooms or wards was needed. In this program, the newborn infants were taken directly from the delivery room to the room or ward with the mother and remained at the mother's bedside at all times unless extraordinary circumstances intervened. Under this regimen there was an increase in the incidence of breast feeding and a decrease in infection among the infants. The mothers were reported to be enthusiastic in accepting the program, and expressed greater confidence in their ability to care for the infants on going home.

In Pennoyer's[9] experiences with an elective rooming-in program that included 522 private and ward patients, the majority of the patients declared themselves enthusiastically in favor of the plan. The mothers were able to participate in a rational and flexible neonatal program without architectural changes in the hospital, additions of nursing personnel or psychiatric help.

Prematurity

Since prematurity is the most significant single cause of infant mortality, a brief review of advances in this phase of pediatrics is desirable. Recent investigations of Barnett[10, 11] and others [12] have shown immaturity of renal function in the full-term newborn infant, as well as in the premature one. This affects administration of drugs, fluids and electrolytes in such conditions as dehydration, acidosis and surgical procedures.

Smith's[13] studies of the adjustment of electrolyte and water balance in newborn premature infants have revealed an excess excretion of sodium and chloride soon after birth; a deficiency in potassium, indicated by its high retention when food is given; and an increased breakdown of body protein. Edema is almost invariably present in premature infants and is considered to be due to minor disturbances in the electrolyte pattern. To sustain survival, it is essential to withhold feedings until edema has disappeared; this may take as long as four days.

Some infants delivered by cesarean section fail to do well, and severe atelectasis develops. Gellis, White and Pfeffer,[14] proposing that these difficulties might result from the swallowing of large amounts of amniotic fluid followed by regurgitation and aspiration, reported the use of gastric suction to remove this fluid. It was found that 3 to 7 cc. of thick mucus could be removed on gastric suction from infants delivered by cesarean section. From infants delivered by section from diabetic mothers, the amounts removed were as much as 14 cc., so that the procedure may certainly be recommended in this group. Maternal diabetes increases the incidence of respiratory complications in the newborn, which are more hazardous than hypoglycemia. Clifford[15] has pointed out that if atelectasis persists beyond three or four days, it is well to start antibiotics in prophylactic doses in an effort to prevent secondary infection.

Retrolental Fibroplasia

The etiology of retrolental fibroplasia has been continually investigated since Terry[16] first noted the correlation of retrolental opacity with prematurity, and yet nothing conclusive has appeared. It has been found in most clinics[17-19] that retrolental fibroplasia generally occurs in premature infants of low birth weight (1360 gm. or less) and at gestational ages of six or seven months. Laupus and Bousquet,[20] reviewing the pathogenesis of the disease on the basis of their ophthalmoscopic examinations of 72 infants whose birth weights were less than 1650 gm., describe the following six stages in the development of retrolental fibroplasia: retinal vascular change, consisting of arterial and venous tortuosity and increased caliber of the veins; rupture of vessels, with formation of preretinal or subhyaloid hemorrhages; extension of the hemorrhage into the vitreous; organization of the hemorrhage; retinal detachment; and partial-to-complete occlusion of the pupil by membrane. In many cases, the acute stages of retrolental fibroplasia do not progress to the end picture of retrolental membranes. In some, as pointed out by Owens and Owens[21] and by Laupus and Bousquet,[20] the process regresses spontaneously and leaves practically no perceptible evidence of the disease. In the series of Owens and Owens evidence of the acute stage was found in approximately 50 per cent of all infants weighing less than 1360 gm. (3 pounds), but the incidence of the complete form of the disease was much lower.

Pointing out a relation between hemangioma and retrolental fibroplasia in a large series of cases, Reese and Block[22] reported the incidence of hemangioma as 18 per cent. Kinsey and Zacharias[23] found no greater incidence of hemangioma when retrolental fibroplasia did not develop.

Studies by Kinsey and others have not proved any relation between retrolental fibroplasia and the amount of iron or multiple vitamins in water-miscible form administered as mentioned in earlier reports. The emulsifying or homogenating agents used in water-soluble vitamin preparations have also been found to be without effect on the incidence of retrolental fibroplasia. Hepner, Krause and Davis[24] observed that early exposure to light had no effect on the incidence.

The spontaneous resolution of the disease in a high percentage of infants affected makes evaluation of any therapeutic agent difficult. Owens and Owens,[21] reporting on the use of vitamin E in premature infants for a period of over two and a half years, found that the incidence of the early phase of retrolental fibroplasia was the same in the infants receiving vitamin E prophylactically as in those not receiving it in a previous period. The

incidence of complete retrolental membranes, however, decreased considerably in the group receiving vitamin E. The effect of vitamin E, if any, seems to be a decrease in the amount of fibrosis and damage during the acute phase of the disease.

Kinsey et al.[25] agree that vitamin E has not proved to be a specific, and its use has generally been abandoned. Kinsey also reports on the effects of weekly blood transfusions of fresh whole blood drawn from mothers in their third trimester of pregnancy on the chance of supplying any factor that might be deficient. He concludes that no element present in whole blood, which can be supplied from the mother, specifically prevents retrolental fibroplasia.

Many reports have appeared on the use of ACTH in retrolental fibroplasia, but definite limitations to therapy with corticotrophin have been encountered. The susceptibility of the infant to infection while under treatment has led to a number of deaths. A safe effective dosage will inhibit growth and may lead to debility if given over for two and a half to three weeks, but the active part of the pathologic process lasts longer than this. Corticotrophin acts to prevent progression of the disease, but it is not curative. Its prolonged use also cause irritability, ravenous appetite, transient edema and tachycardia. The report of Blodi and his associates[26] on the use of ACTH summarizes the opinions and findings of most investigators, emphasizing the fact that ACTH has not proved of benefit in retrolental fibroplasia.

Hepner[27] recently reported that a condition similar to the early retinal stage of retrolental fibroplasia, together with the persistence of the ocular embryonic vascular system, was experimentally produced by administration of repeated massive blood transfusions to kittens rendered edematous by infusions of saline solution. Although a similarity in histopathology between the animal studies and human studies is noted, definite conclusions regarding similarity of etiology cannot yet be made.

Erythroblastosis

Many reports have appeared since Diamond's first article on exchange transfusions in the treatment of hemolytic disease of the newborn due to isoimmunization with Rh and ABO incompatibility. Exchange transfusion has become the accepted method of treatment in the more severe forms of this disease; in the mild cases, simple transfusions may be sufficient. In a recent report on the results of a control study of 477 infants with hemolytic disease of the newborn treated by one of several predetermined methods according to a system of random numbers, Mollison et al.[28] concluded that infants treated with exchange transfusion had a greater chance of survival than those treated by simple transfusion. The improvement produced by exchange transfusion was clearly evident in mature infants who were severely affected (umbilical-cord hemoglobin concentration of less than 11 gm. per 100 cc.), and more strikingly in immature infants who were only moderately affected (umbilical-cord hemoglobin concentration of more than 11 gm.). Immature infants who were severely affected (umbilical-cord hemoglobin concentration of less than 11 gm.) had a low survival rate even when treated by exchange transfusion. The authors also stated that if a woman has lost a child from hemolytic disease of the newborn it is advisable to treat her next infant with exchange transfusion regardless of the mildness of the disease. They reported a decreased incidence of kernicterus in infants treated with exchange transfusion.

Investigations aimed at eliminating maternal immunization factors have been unsuccessful. In reviewing cases treated during the years 1937 to 1948 Vaughan et al.[29] reported that the changing character of the case material made interpretation of the low mortality rates extremely difficult. He found that termination of pregnancy before thirty-eight weeks of gestation increased the risk of kernicterus, and this was corroborated by the study of Mollison and his co-workers.[28] Regarding prognosis in relation to clinical and serologic manifestations at birth, Diamond and his associates[30] report the following results of their studies over a three-year period (1945 to 1948). The prognosis is good in the first Rh-positive infant born to a mother after sensitization to the Rh factor, 30 per cent of such infants showing no clinical evidence of the disease. Approximately 30 per cent of those whose mothers have a titer of less than 1:16 have no disease. As maternal titers rise to 1:64 or higher the prognosis becomes less favorable, and the risk of kernicterus in the infants increases. In affected infants after the first, the prognosis is less favorable, about 40 per cent being stillborn. There is no significant tendency to increasing severity of hemolytic disease after the second affected baby. If a previous infant has had kernicterus, early termination of a later pregnancy is contraindicated because of the relation between immaturity and the familial tendency of kernicterus. Icterus of the skin and scleras at the time of delivery was not seen in an infant with erythroblastosis. Absence of jaundice at birth is thus without value in prognosis; but jaundice may develop as early as one hour after birth and may become prominent after six hours. In Diamond's series, jaundice persisted longer in infants with kernicterus than in those recovering without this complication. With anemia and hepatosplenomegaly developing and increasing soon after birth, the death rate increased, chiefly within the first day of life, with no evidence of kernicterus. This accounted for the mortality of about 50 per cent in the group of infants with hepatosplenomegaly and red-cell counts of less than 2,000,000. An antibody titer of the infant's blood is only of limited prognostic significance since absence of antibodies

does not always mean a favorable prognosis, nor was a high titer necessarily a serious omen. In general, the lower the baby's titer by comparison with the mother's (fetal-maternal-titer ratio), the sicker the baby. For example, if the maternal titer is 1:64 and the infant's titer 0, the disease is usually severe. When there is difficulty in demonstrating agglutination of the infant's cells with anti-Rh serums, tests must be done for blocking antibodies. The Coombs test is positive in practically all Rh-positive infants of sensitized Rh-negative mothers. Male infants have more severe disease and a greater incidence of kernicterus than female.

Vaughan, Allen, and Diamond[31] reported that most infants with kernicterus seemed in good condition at birth, with normal neurologic reactions; pathological examination of stillborn fetuses gave no evidence of kernicterus. Delivery of infants with erythroblastosis before term increased the likelihood of kernicterus. Thus, kernicterus was thought to be a disease of neonatal life not necessarily dependent on changes that might have taken place before birth. The signs were so characteristic that the diagnosis could be made or discarded by the end of the first week of life. On the basis of physical findings and observation in erythroblastosis, death between the first and sixth days of life was usually associated with kernicterus. There was progressively increasing jaundice during the first three days. After the first day, the following were noted: lethargy, poor feeding, refusal of feedings, vomiting, disappearance of the Moro reflex and tendency to opisthotonos with the arms rigidly extended and inwardly rotated with fists clenched when stimulated to startle. A high-pitched cry usually followed, with lethargy and relative atonia supervening. Death during this period was preceded by irregular gasping respirations, cyanosis and the appearance of frothy bloody material in the respiratory tract. Infants with kernicterus who survived showed motor defects of the extrapyramidal tract, usually with mental retardation.

Allen, Diamond and Vaughan[32] have also reported that exchange transfusion has lowered the incidence of kernicterus. Failure to terminate pregnancy early in sensitized mothers has not significantly increased the number of stillbirths. The use of blood from female donors is apparently of value in helping the child through the hazardous first hours of life. The following criteria for exchange transfusions have been set forth[33]: pallor, hepatosplenomegaly, petechiae, edema or a red-cell count of less than 4,500,000 in an Rh-positive infant of a sensitized Rh-negative mother; an Rh-positive baby without clinical signs but with a maternal antibody titer of 1:16 or higher; an immature Rh-positive baby of a sensitized mother, even without clinical signs of disease; or an Rh-positive baby without clinical signs but with a history of severe erythroblastosis in a previous sibling, especially if the previous infant had kernicterus. Hsia et al.[34] report a correlation between a high incidence of kernicterus and high serum bilirubin levels. Kernicterus does not occur if the serum bilirubin level is kept below 15 mg. per 100 cc. With levels of over 35 mg. per 100 cc., most infants show signs of kernicterus. If, after an initial exchange transfusion, the serum bilirubin has risen above 20 mg. per 100 cc. or will predictably exceed that level, a second exchange is indicated as soon as such information is obtained.

Pancreatic Fibrosis

In 1949 Shwachman, Patterson and Laguna[35] reported a simple, practical clinical test for screening infants in whom pancreatic fibrosis is suspected. The test depends on the liquefaction and digestion of gelatin on an x-ray film by a stool containing trypsin. Although the test is not infallible, its simplicity and comparatively high validity in infants makes it a useful clinical procedure.

Johnstone and Neter[36] have recently pointed out that gelatin-liquefying bacteria, of which *Pseudomonas aeruginosa* is the commonest, may give a false-positive test. They have found this group of bacteria on culture of duodenal juice in a high percentage of cases, which leaves the results of duodenal intubation studies open to error. Johnstone[37] has suggested the use of a soybean-trypsin inhibitor to inactivate tryptic activity and allow the measurement of proteolytic activity beyond the point of bacterial gelatinase activity. As pointed out by Shwachman et al., the gelatin film test is a screening test, and negative results should indicate the desirability of performing duodenal intubation when the clinical findings indicate pancreatic fibrosis as a diagnostic possibility.

More recently, Shwachman and Patterson[38] have demonstrated increased viscosity of the duodenal juice as measured by the Ostwald viscosimeter in patients with pancreatic fibrosis. The normal viscosity of duodenal juice as measured by the Ostwald viscosimeter is less than three minutes. In their series, the viscosity was significantly increased in approximately 90 per cent of the patients with pancreatic fibrosis, and the authors pointed out that this is another valuable diagnostic test to be used in the study of such patients. Absence or reduction of trypsin in the duodenal juice with an increase in viscosity is characteristic of the disease.

Bronchiectasis is a common sequela of pancreatic fibrosis. The newer antibiotics such as aureomycin and terramycin, as suggested by Shwachman et al.,[39] have become important therapeutic agents in the treatment of this complication.

It has been observed that prolonged antibiotic therapy tends to produce a change in the bacterial flora of the respiratory and gastrointestinal tracts, with the emergence of resistant strains of organisms

not susceptible to therapy. Pseudomonas particularly dominates these floras.

Fluid Balance

Recent investigations of Darrow and his associates,[40] Gamble, [41, 42] and others[43-48] have drawn attention to the importance of the potassium ion in electrolyte balance and to the necessity for the correction of intracellular deficits in fluid and electrolyte therapy. Abnormalities in the concentration of cations in the intracellular fluid may result in disturbed physiology. The potassium ion, which is present in high concentration in intracellular fluid, is the chief regulator of the content of water and is apparently intimately related to acid-base balance. Loss of intracellular potassium and resulting hypokaliemia occurs in infantile diarrhea and after continuous intravenous infusions of potassium-free fluids in the treatment of dehydration. The serum potassium concentration often drops after such therapy because of the dilution of extracellular fluid and the increase in the renal loss of potassium concomitant with the increase in excretion of urine since the kidney is slow in conserving potassium. Acidosis is accompanied by loss of intracellular potassium when there are also deficiencies of water and electrolytes.[49, 50]

Abnormal losses of potassium also occur when gastrointestinal secretions are removed through fistulas or through suction drainage from catheters introduced into the stomach and small intestine. In addition, cells tend to lose potassium and to gain sodium when the circulation is impaired in dehydration or shock or when there is tissue anoxia. This transfer of potassium from intracellular to extracellular fluid, and subsequent urinary excretion, may depend on increased activity of the adrenal cortex in response to stress. In general, it appears that the loss of potassium from cells results in partial replacement of this ion by sodium. The studies of Darrow[50] indicate that the loss of potassium and ensuing events in some way result in an acid-base disturbance characterized by the development of hypochloremic alkalosis, and that when alkalosis and potassium deficiency occur together, physiologic saline solution is not sufficient and potassium solutions should be given as well.

Gastric juice contains relatively more chloride than sodium, as well as appreciable amounts of potassium. The gastric contents may contain an excess of chloride over sodium, and loss of such acid gastric juices will leave the body with a relative excess of sodium available to form bicarbonate. This type of alkalosis is seen in pyloric obstruction. As pointed out above, when it is complicated by a potassium deficiency that is due to the loss of potassium in gastric contents as the result of vomiting, the administration of potassium-containing solutions will be necessary to correct the deficit. In such a case alkalosis may therefore continue despite the administration of sodium and chloride, which seem to facilitate the excretion of potassium by the kidney.[51]

Recent emphasis on potassium and its importance in infantile diarrhea should not obscure the well known fact that, in addition to deficits of potassium, deficits of water, sodium and chloride occur.

Atchley et al.,[52] in 1933, and, more recently, Danowski[53] and others have pointed out that during the development of diabetic acidosis, glucose and ketone bodies are excreted in large quantities and polyuria develops. Hypokaliemia results from the loss of potassium during this period. Treatment of the acidosis is conducive to the production of hypokaliemia. The excess in loss of potassium over the loss of nitrogen as the patient lapses into coma is due partly to the breakdown of glycogen and partly to the rapid excretion of ketone acids in the form of potassium salts. Dehydration also causes a further loss of intracellular potassium. In the treatment of diabetic coma the administration of insulin results in the deposition of glycogen in the cells, requiring a transfer of extracellular potassium into the cells. With vigorous insulin therapy in diabetic acidosis, the withdrawal of potassium from the extracellular fluid may be of sufficient degree to cause a fall in serum potassium to a level sometimes productive of respiratory paralysis and cardiac damage. Several authors[54-56] have pointed out that hypokaliemia is a definite danger to patients recovering from diabetic acidosis and that the reduction of sodium salts, together with the administration of potassium salts, is of the utmost importance. The time of administration of potassium solutions in the treatment of diabetic acidosis is important. After four to six hours of therapy, when the flow of urine has increased, it is usually safe to give potassium slowly. Once the patient is able to eat, potassium replacement from oral intake will be adequate.

Burns and crushing injuries to muscles produce symptoms of loss of extracellular water and electrolytes at the sites of tissue injury or exudate. It has been shown that there is accumulation and immobilization of extracellular water and electrolytes at the site of injury, and although they may not be from the body they are not available to the rest of the tissues.

Of the three ions, sodium, potassium and chloride, only potassium seems to alter cellular function by specific ionic effects. Low concentration of potassium in the serum is accompanied by definite symptoms, signs and electrocardiographic changes, all of which can be abolished by the administration of potassium. The symptoms and signs of hypokaliemia have been described by Darrow and Pratt[57] as follows: weakness and hypotonia of skeletal muscles, progressing to frank paralysis; dyspnea, with gasping respiration and evidence of use of the accessory muscles of respiration; cyanosis;

abdominal distention; nausea and vomiting; cardiac enlargement and appearance of systolic murmurs; increased pulse pressure, with Corrigan's pulse; and elevated venous pressure and signs of cardiac failure. The electrocardiographic changes accompanying low serum concentrations of potassium are slightly prolonged QT intervals, decreased height and inversion of P waves, extrasystoles and auriculoventricular block. It is well to point out that cortisone therapy is often accompanied by hypokaliemia and that the administration of potassium chloride is necessary in many patients during the course of therapy. Without renal insufficiency, hyperkaliemia is unlikely to develop.

In the light of the information presented by the recent investigations that have been reviewed, it is obvious that intracellular deficits as well as extracellular deficits of electrolytes and water should be considered in fluid therapy.[58]

Immunization

In the field of immunology, increasing evidence has accumulated that the young infant is capable of responding to antigens with formation of antibodies when passive immunity does not exist. Sako,[59-61] Miller,[62, 63] Sauer,[64] Disant'Agnese,[65-67] Cooke,[68] Bell[69] and others have reported their favorable results when combined antigen was administered beginning as early as the third month.

The Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases of the American Academy of Pediatrics has recently presented its recommendations for immunizations. It has recommended that all infants be actively immunized against diphtheria, pertussis and tetanus, with a course of injections of combined alum-precipitated or aluminum-hydroxide-adsorbed diphtheria and tetanus toxoids containing *Haemophilus pertussis* vaccine. These materials have a more prolonged antitoxic immunity, are more effective as immunizers against pertussis in early infancy and produce fewer systemic reactions because they have a lower protein content and are absorbed more slowly than the fluid toxoids.

Combined immunization should be started in children three months old. The following schedule of immunization has been recommended by the Committee:

Three months: 0.5 cc. of alum-precipitated, or aluminum-hydroxide-adsorbed diphtheria and tetanus toxoids containing 15 billion *H. pertussis* given intramuscularly in the left gluteus maximus muscle.

Four months: Repeat in right gluteus maximus muscle.

Five months: Repeat in left vastus lateralis or right deltoid muscle.

Six months: Smallpox vaccination over left deltoid muscle.

Ten to twelve months: Schick test.

The volume of any one injection should be limited to 0.5 cc., given intramuscularly at intervals of not less than a month and preferably not more than three months, but injections at intervals prolonged even up to six months rarely interfere with the final immunity.

Primary immunization of children not immunized in infancy should be carried out with the same dosage and schedule described except that the deltoid and triceps muscles, instead of the gluteal muscles, should be injected.

Booster or recall injections in one dose of 0.5 cc. of combined triple antigen should be given a year after completion of the primary course. Another booster of 0.3 cc. should be given two years later — that is, three years after completion of the primary course, when the child is about three or four years old. Recall injections of 0.3 cc. every three years thereafter have been recommended. Thus, these should be given at six or seven years of age and at nine or ten years of age. Congenital heart disease is not a contraindication to immunization.

Recent reports[70-74] from Australia, England and this country have indicated that in patients who received an injection of antigen during the month prior to onset of poliomyelitis there is a close correlation between the site of paralysis and the site of injection. Such a correlation is not apparent in patients with poliomyelitis who received the injection of antigen more than a month prior to onset of the disease. This question is now under investigation; because of its serious implications, the presence of poliomyelitis in epidemic proportions warrants postponement of injections and vaccinations. If diphtheria, pertussis and smallpox are not prevalent, it is recommended that these injections be delayed until the incidence of poliomyelitis in the community has decreased.

(*To be concluded*)

References

1. Smith, R. M. Fifty years of medical progress: medicine as science: pediatrics. *New Eng. J. Med.* **244**:176-181, 1951.
2. Mid-Century White House Conference, 1951.
3. American Academy of Pediatrics. *Child Health Services and Pediatric Education: Report of Committee for the Study of Child Health Services.* 270 pp. New York: The Commonwealth Fund, 1949.
4. American Board of Pediatrics. Statement on training requirements in growth and development. *Pediatrics* **7**:430, 1951.
5. Olmsted, R. W., Svibergson, R. I., and Kleeman, J. A. Value of rooming-in experience in pediatric training. *Pediatrics* **3**:617-621, 1949.
6. Klatskin, E. H., Lethin, A. N., and Jackson, E. B. Choice of rooming-in or newborn nursery: analysis of data from prenatal screening interviews of 1251 mothers, relating to their choice of hospital accommodation for their infants in rooming-in unit or in newborn nursery. *Pediatrics* 6:878-889, 1950.
7. Reid, D. E., and Cohen, M. E. Evaluation of present-day trends in obstetrics. *J. A. M. A.* **142**:615-623, 1950.
8. McBryde, A. Compulsory rooming-in in ward and private newborn service at Duke Hospital. *J. A. M. A.* **145**: 625-628, 1952.
9. Pennoyer, M. M. M. Experiences with elective rooming-in program. *J. Pediat.* **38**:213-220, 1951.
10. Barnett, H. L., Hare, K., McNamara, H., and Hare, R. Measurement of glomerular filtration rate in premature infants. *J. Clin. Investigation* **27**:691-699, 1948.

11. Barnett, H. L. Kidney function in young infants. *Pediatrics* **5**: 171-179, 1950.
12. McCance, R. A. Renal function in early life. *Physiol. Rev.* **28**: 331-348, 1948.
13. Smith, C. A., Yudkin, S., Young, W., Minkowski, A., and Cosnman, M. Adjustment of electrolytes and water following premature birth (with special reference to edema). *Pediatrics* **3**:34-48, 1949.
14. Gellis, S. S., White, P. W., and Pfeffer, W. Gastric suction: proposed additional technic for prevention of asphyxia in infants delivered by cesarean section: preliminary report. *New Eng. J. Med.* **240**: 533-537, 1949.
15. Clifford, S. H. Fetal anoxia at birth and cyanosis of newborn: differential diagnosis and management. *Am. J. Dis. Child.* **76**: 666-678, 1948.
16. Terry, T. L. Extreme prematurity and fibroplastic overgrowth of persistent vascular sheath behind crystalline lens. *Am. J. Ophth.* **25**:203, 1942.
17. Exline, A. L., and Harrington, M. R. Retrolental fibroplasia: clinical statistics from premature center of Charity Hospital of Louisiana at New Orleans. *J. Pediat.* **38**:1-7, 1951.
18. Dancis, J., Lewis, J. M., and Guy, L. P. Retrolental fibroplasia. *New Eng. J. Med.* **245**:402-406, 1951.
19. Heath, P. Retrolental fibroplasia in cyandrome: pathogenesis and classification. *Arch. Ophth.* **44**:245-274, 1950.
20. Laupus, W. E., and Bousquet, F. P. Retrolental fibroplasia: role of hemorrhage pathogenesis. *Am. J. Dis. Child.* **81**:617-626, 1951.
21. Owens, W. C., and Owens, E. U. Retrolental fibroplasia of premature infants. II. Studies on prophylaxis of disease: use of alpha tocopheryl acetate. *Am. J. Ophth.* **32**:1631-1637, 1949.
22. Reese, A. B., and Block, F. C. Retrolental fibroplasia. *Am. J. Ophth.* **34**:1-24, 1951.
23. Kinsey, V. E., and Zacharias, L. Retrolental fibroplasia: incidence in different localities in recent years and correlation of incidence with treatment given infants. *J. A. M. A.* **139**:572-578, 1949.
24. Hepner, W. R., Krause, A. C., and Davis, M. E. Retrolental fibroplasia and light. *Pediatrics* **3**:824-828, 1949.
25. *Report on the Second M. & R. Pediatric Research Conference: Retrolental fibroplasia.* 59 pp. Columbus, Ohio: M & R Laboratories, 1952.
26. Blodi, F. C., Silverman, W. C., Day, R., and Reese, A. B. Experiences with corticotropin (ACTH) in acute stage of retrolental fibroplasia. *Am. J. Dis. Child.* **82**:242-245, 1951.
27. Hepner, W. R., Jr. Retrolental fibroplasia: animal studies: induced vascular engergement and hyperplasia of iris tunica vasculosa lentes and retina in kittens. *Pediatrics* **9**:602-606, 1952.
28. Mollison, P. L., Walker, W., Camb, M. D., and Dunrh, M. D. Controlled trials of treatment of hemolytic disease of newborn. *Lancet* **1**:429-433, 1952.
29. Vaughan, V. C., III, Allen, F. H., Jr., and Diamond, L. K. Erythroblastosis fetalis. I. Problems in interpretation of changing mortality in erythroblastosis fetalis. *Pediatrics* **6**:173-182, 1950. II. Prognosis in relation to history, maternal titer and length of fetal gestation. *Ibid.* Pp. 441-449.
30. Diamond, L. K., Vaughan, V. C., III, and Allen, F. H., Jr. Erythroblastosis fetalis. III. Prognosis in relation to clinical serologic manifestations at birth. *Pediatrics* **6**:630-637, 1950.
31. Vaughan, V. C., III, Allen, F. H., Jr., and Diamond, L. K. Erythroblastosis fetalis. IV. Further observation of kernicterus. *Pediatrics* **6**:706-716, 1950.
32. Allen, F. H., Jr., Diamond, L. K., and Vaughan, V. C., III. Erythroblastosis fetalis. VI. Prevention of kernicterus. *Am. J. Dis. Child.* **80**:779-791, 1950.
33. Diamond, L. K., Allen, F. H., Jr., and Thomas, W. O., Jr. Erythroblastosis fetalis. VII. Treatment with exchange transfusion. *New Eng. J. Med.* **244**:39-49, 1951.
34. Hsia, D. Y., Allen, F., Gellis, S., and Diamond, L. Erythroblastosis fetalis. VIII. Studies of serum bilirubin levels in relation to kernicterus. *New Eng. J. Med.* **247**:668-671, 1952.
35. Shwachman, H., Patterson, P. R., and Laguna, J. Studies in pancreatic fibrosis: simple diagnostic gelatin film test for stool trypsin. *Pediatrics* **4**:222-230, 1949.
36. Johnstone, D. E., and Neter, E. Studies on laboratory diagnosis of cystic fibrosis of pancreas: positive gelatin film tests due to gelatin-liquefying bacteria in feces and duodenal juice. *Pediatrics* **7**: 483-490, 1951.
37. Johnstone, D. E. Studies on gelatin-liquefying properties of certain bacteria: with particular reference to laboratory diagnosis of cystic fibrosis of pancreas. *Pediatrics* **6**:351-356, 1950.
38. Shwachman, H., and Patterson, P. R. Progress in study of "mucoviscidosis" (pancreatic fibrosis) with illustrative case presentations. *Pediatrics* **7**:153-163, 1951.
39. Shwachman, H., Crocker, A. C., Foley, G. E., and Patterson, P. R. Aureomycin therapy in pulmonary involvement of pancreatic fibrosis (mucoviscidosis). *New Eng. J. Med.* **241**:185-192, 1949.
40. Darrow, D. C., Pratt, E. L., Flett, J., Jr., Gamble, A. H., and Wiese, H. F. Disturbances of water and electrolytes in infantile diarrhea. *Pediatrics* **3**:129-156, 1949.
41. Gamble, J. L. *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid.* Fifth edition. 113 pp. Cambridge, Massachusetts: Harvard University Press, 1949.
42. *Idem.* Deficits in diarrhea. *J. Pediat.* **30**:488-494, 1947.
43. Flett, J., Pratt, E., and Darrow, D. Methods used in treatment of diarrhea with potassium and sodium salts. *Pediatrics* **4**:604-619, 1949.
44. Butler, A. M., and Talbot, N. B. Parenteral-fluid therapy. I. Estimation and provision of daily maintenance requirements. *New Eng. J. Med.* **231**:585-590, 1944. II. Estimation of losses incident to starvation and dehydration with acidosis or alkalosis and provision of repair therapy. *New Eng. J. Med.* **231**:621-628, 1944.
45. Marquardt, G. H. Recent developments in treatment of acidosis. *M. Clin. North America* **32**:264-271, 1948.
46. Rapoport, S., Dodd, K., Clark, M., and Syllm, L. Hyperosmolarity and hyperelectrolytemia in pathologic conditions of childhood. *Am. J. Dis. Child.* **74**:682-702, 1947.
47. Govan, C. D., Jr., and Darrow, D. C. Use of potassium chloride in treatment of dehydration of diarrhea in infants. *J. Pediat.* **28**: 541-549, 1946.
48. McBryde, A., Mulherin, P. A., Harris, J. S., and London, A. H. Management of infantile diarrhea and dysentery. *Pediatrics* **2**: 335-348, 1948.
49. Goettsch, E., Lippman, R. W., Luetscher, J. A., Bates, T., and Peterman, M. G. Round-table discussion: certain electrolyte disturbances in renal insufficiency. *Pediatrics* **5**:147-156, 1950.
50. Darrow, D. C. Body-fluid physiology: role of potassium in clinical disturbances of body water and electrolyte. *New Eng. J. Med.* **242**:978-983 and 1014-1018, 1950.
51. Burnett, C. H., Burrows, B. A., Commons, R. R., and Towery, B. T. Studies of alkalosis. II. Electrolyte abnormalities in alkalosis resulting from pylcric obstruction. *J. Clin. Investigation* **29**: 175-186, 1950.
52. Atchley, D. W., et al. On diabetic acidosis: detailed study of electrolyte balances following withdrawal and reestablishment of insulin therapy. *J. Clin. Investigation* **12**:297-326, 1933.
53. Danowski, T. S. Present ideas concerning body fluids and chief electrolytes. *Pennsylvania M. J.* **43**:494-496, 1950.
54. Nicholson, W. M., and Branning, W. S. Potassium deficiency in diabetic acidosis. *J. A. M. A.* **134**:1292-1294, 1947.
55. Martin, H., and Wertman, M. Serum potassium, magnesium, and calcium levels in diabetic acidosis. *J. Clin. Investigation* **26**: 217-228, 1947.
56. Holler, J. W. Potassium deficiency occurring during treatment of diabetic acidosis. *J. A. M. A.* **131**:1186-1189, 1946.
57. Darrow, D. C., and Pratt, E. L. Fluid therapy: relation to tissue composition and expenditure of water and electrolyte. *J. A. M. A.* **143**:365-373 and 432-439, 1950.
58. Hand, A. M., and Leininger, C. R. Parenteral fluid therapy in children. *M. Clin. North America* **34**:53-70, 1950.
59. Sako, W. Practical and immunologic aspects of pediatric immunizations. *Pediatrics* **2**:722-730, 1948.
60. Sako, W., Treuting, W. L., Witt, D. B., and Nichamin, S. J. Early immunization against pertussis with alum precipitated vaccine. *J. A. M. A.* **127**:379-383, 1945.
61. Sako, W. Studies on pertussis immunization. *J. Pediat.* **30**:29-40, 1947.
62. Miller, J. J., Jr. Immunization procedures in infancy. *Post-Grad. M. J.* **9**:160-163, 1951.
63. Miller, J. J., Jr., and Ryan, M. L. Immunization with combined diphtheria and tetanus toxoids (aluminum hydroxide absorbed) containing H. pertussis vaccine: duration of serologic immunity. *Pediatrics* **1**:8-22, 1948.
64. Sauer, L. W., Tucker, W. H., and Markley, E. Immunity responses to mixtures of diphtheria toxoid and pertussis vaccine. *J. A. M. A.* **125**:949-952, 1944.
65. Disant' Agnese, P. A. Combined immunization against diphtheria tetanus, and pertussis in newborn infants. I. Production of antibodies in early infancy. *Pediatrics* **3**:20-33, 1949.
66. *Idem.* Combined immunization against diphtheria, tetanus, and pertussis in newborn infants. II. Duration of antibody levels. Antibody titers after booster dose. Effect of passive immunity to diphtheria on active immunization with diphtheria toxoid. *Pediatrics* **3**:181-193, 1949.
67. *Idem.* Combined immunization against diphtheria tetanus and pertussis in newborn infants. III. Relationship of age to antibody production. *Pediatrics* **3**:333-344, 1949.
68. Cooke, J. V., Holowach, J., Atkins, J. E., and Powers, J. R. Antibody formation in early infancy against diphtheria and tetanus toxoids. *J. Pediat.* **33**:141-146, 1948.
69. Bell, J. A. Pertussis immunization: use of two doses of alum precipitated mixture of diphtheria toxoid and pertussis vaccine. *J. A. M. A.* **137**:1276-1281, 1948.
70. *Report of the Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases of the American Academy of Pediatrics.* 69 pp. Evanston, Illinois: American Academy of Pediatrics, 1951.
71. Martin, J. K. Local paralysis in children after injections. *Arch. Dis. Child.* **25**:1-14, 1950.
72. McCloskey, B. P., Relation of prophylactic inoculations to onset of poliomyelitis. *Lancet* **1**:569-663, 1950.
73. Hill, A. B., and Knowelden, J. Inoculation and poliomyelitis: statistical investigation in England and Wales in 1949. *Brit. M. J.* **2**:1-6, 1950.
74. Anderson, G. W., and Skaar, A. E. Poliomyelitis occurring after antigen injections. *Bull. Univ. Minn. Hosp. & Minn. M. Found.* **22**:359-370, 1951.

MEDICAL INTELLIGENCE

SUPRAVENTRICULAR TACHYCARDIA IN THE FETUS*

Report of a Case

SALVATORE M. SANCETTA, M.D.,†
THOMAS H. REDDING, M.D.,‡ AND
WILLIAM S. HAUBRICH, M.D.§

CLEVELAND, OHIO

USING phonocardiography, Hyman[1] found that cardiac arrhythmias are not uncommon in the fetus. These he divided into the following three types:

Sinus arrhythmia and changes in intensity of the heart sounds, the latter conditioned by resonant factors within the maternal abdomen, owing to rhythmic changes in uterine contractions, and most common in the latter part of pregnancy.

Interruptions of a regular rhythm, shown electrocardiographically after birth to represent noneffective premature beats of the right ventricle. In 6 cases all had disappeared by the eighth day, and in no case was an abnormality of the heart found, although the association of prenatal premature beats with congenital heart disease has been reported by others.[2-4]

A gross irregularity, thought to represent auricular fibrillation, though in the 8 newborn babies who survived birth this was not shown to exist electrocardiographically. In the remaining 3 children, who did not survive birth, abortion, miscarriage and difficult resuscitation caused death. The fetal heart rates varied between 92 and 160, 148 and 210, and 120 and 200, respectively; Hyman conjectured that such an arrhythmia may predispose to the complications listed.

Not mentioned by Hyman are two fetal arrhythmias that may be listed under his third category as bearing some importance from the standpoint of recognition and therapy — namely, heart block (complete or partial), and supraventricular tachycardia (auricular and nodal tachycardia, or auricular flutter). Several cases of complete[5-11] and partial[2,-12-15] heart block have been reported, as well as at least 2 cases of auricular flutter[16,17]: 1 of nodal[18] and 1 of supraventricular[19] tachycardia, which was also observed in the case reported below.

*From the departments of Medicine and Obstetrics, Western Reserve University School of Medicine, City Hospital Division.

†Instructor in medicine, Western Reserve University School of Medicine.

‡Demonstrator in obstetrics and gynecology, Western Reserve University School of Medicine; clinical assistant obstetrician and gynecologist, St. Luke's Hospital.

§Formerly, resident in medicine, Cleveland City Hospital.

CASE REPORT

C. T., a 21-year-old Negress, a gravida 3, para 2, had the onset of labor on November 15, 1950, at 5 a.m., 4 days after the predicted date. The patient had been followed in the maternal clinic of another hospital; when last seen she appeared normal, and the fetal heart rate was 130. This information was not available to the obstetric staff at this hospital when she was admitted early in the second stage of labor at 9:00 p.m. At that time the blood pressure was 140/90 and there was some edema of the legs; she was thought to have mild pre-eclampsia. In addition, an acute pyelonephritis was found after delivery. The fetal heart rate was estimated to be about 240; the rhythm, as far as could be discerned, was quite regular. Both rate and rhythm remained unchanged during 3 hours' observation. Fetal anoxia could not be ruled out. At 1:07 on the next morning a normal male infant, weighing 7 pounds, 11 ounces, was delivered uneventfully by cesarean section. The baby appeared quite normal; the heart rate was about 240. An electrocardiogram was taken at 2:00 a.m.; the heart rate was 222, and the abnormality was interpreted as supraventricular tachycardia. Unilateral carotid-sinus pressure was ineffective, but bilateral application terminated the arrhythmia. Unfortunately, the child was not under electrocardiographic observation at the time, and the transition was not recorded; a second record taken at 2:40 a.m. revealed a basic sinus mechanism and a heart rate of 150. A third record, obtained at 10:00 a.m., revealed persistence of the sinus mechanism with a heart rate of 130 (Fig. 1).

When seen again at the age of 9 months, the child was developing normally and there was no evidence of abnormality on physical examination; the electrocardiogram and chest x-ray film were normal.

DISCUSSION

When information about the fetal rate and rhythm prior to labor is not available, as in the case reported above, there is little choice of management. Previous knowledge of either heart block with a slow rate or tachycardia, contrariwise, does not preclude expectant management and spontaneous labor.

Clinical recognition of these facts is important. Phonocardiography does not offer diagnostic superiority; fetal electrocardiography, by means of either maximal amplification of a standard electrocardiograph or the much more sensitive electroencephalograph adapted as described by Blondheim,[20] does not afford sufficient amplification to record P waves and hence is of no value in the study of arrhythmias. The electroencephalograph yields a fetal tracing by the sixteenth week of intrauterine life, much before the standard electrocardiograph, and has its greatest value in the determination of fetal life when a previously detected heart beat can no longer be heard, since false-positive results do not occur and the biologic tests may remain positive for weeks after death of the fetus. The diagnosis of the nature of fetal arrhythmias then rests on clinical grounds, a heart rate persistently below 80 indicating block, one above 160 and showing great variation, to rates well above 200, indicating

tachycardia not of sinus origin. These criteria do not apply when observations are made for the first time during labor, although failure of the heart rate to vary with uterine contractions in this situation is some argument against fetal anoxia.

The prognosis appears to be worst in cases of heart block. In 7 cases of complete heart block reported in the literature, death attended by cyanosis occurred in 3 at the end of six,[9] eighteen[11] and seventy-five[10] days of life; congenital heart disease was present in 1 infant still living at the age of twelve months,[7] 2 were living and well (without heart disease) at the age of five months with persistence of the block,[5, 8] and 1 was quite well and normal at the age of eleven months when the arrhythmia disappeared.[6] In an additional case,[3] manifesting an unusual intrauterine trigeminy, the electrocardiogram on the fifth day of life was interpreted as showing blocked auricular premature beats; the child at the age of nine months was still living, but there was unmistakable evidence of congenital heart disease. Additional cases of congenital heart disease diagnosed in utero by auscultation of fetal murmurs in association with frequent premature beats have been reported[2, 4]; in a third case, in which no murmur was heard, the premature beats disappeared on the sixth day of life and the child was normal.[21] These cases may fall into the group that Hyman[1] assumed to be auricular fibrillation. No therapy is of much value in these patients.

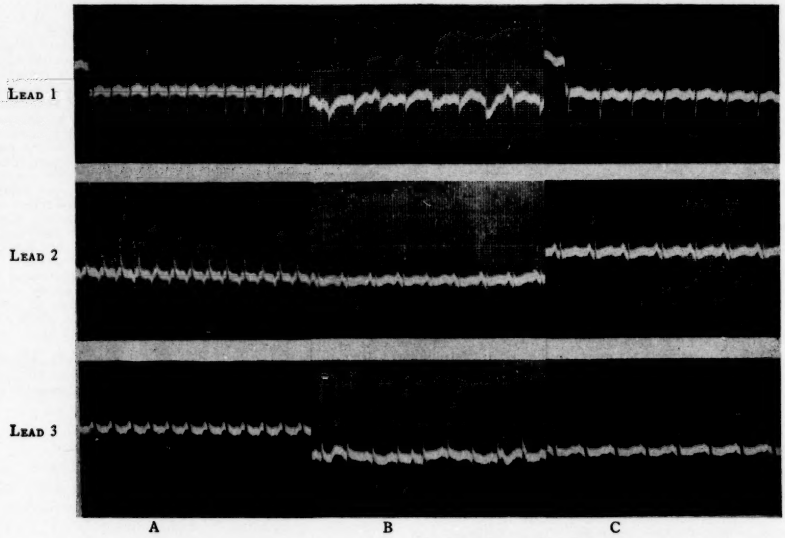


FIGURE 1. *Electrocardiograms in a Case of Supraventricular Tachycardia.*
A. *Record taken fifty-seven minutes after birth. The heart rate is about 222; Lead 2 is suggestive of high nodal tachycardia.*
B. *Electrocardiogram forty minutes after record A. Carotid-sinus pressure had been applied about fifteen minutes before. The basic mechanism is sinus; at least one nodal beat is seen in Lead 3. The heart rate is 150.*
C. *Record made nine hours after birth. The heart rate is now 130.*

For the management of supraventricular tachycardias not due to fetal distress, therapy is available, mandatory and effective. In 5 cases, including the case reported above, the arrhythmias yielded to digitalis,[16, 17, 19] quinidine[18] or carotid-sinus pressure. The last was ineffective in the cases reported in the literature, but it interrupted the arrhythmia permanently in our patient; it is usually without value in infants and young children[22] but deserves trial. The drug of choice is digitalis, administered parenterally as Digifolin or Digalen if the arrhythmia persists more than a few hours after birth or if cardiorespiratory distress is present early — 0.05

gm. may be given intramuscularly, repeated in six hours and continued in doses of 0.025 gm. every twelve hours for several days; a maintenance dose of 0.05 gm. daily may then be indicated and therapy begun again at a later date if there is a recurrence. In the case reported by Garvin and Kline[18] digitalis was only partially and temporarily effective, but quinidine in amounts of 10, 20 and 30 mg. given orally four times daily on the fifth, sixth and seventh days was eventually effective in interrupting auricular flutter. The doses of both digitalis and quinidine mentioned represent conservative average amounts and are quite safe.

The importance of recognition and treatment of tachycardia rests in the susceptibility of such infants to congestive heart failure, particularly when interference with ventricular filling may be extreme. Hubbard[22] emphasizes the fact that neglect to recognize congestive heart failure may lead to faulty diagnoses of pneumonia or idiopathic cardiac hypertrophy, with a fatal termination. In the cases of supraventricular tachycardia originating in utero, treatment was uniformly and permanently effective, and no heart disease was found during the follow-up periods.

Summary

A fifth case of supraventricular tachycardia in utero is added to those previously reported in the literature. The attack was terminated during the second hour of life by bilateral carotid-sinus pressure.

The nature, diagnosis, prognosis and treatment of fetal arrhythmias are discussed.

References

1. Hyman, A. S. Irregularities of foetal heart. *Am. J. Obst. & Gynec.* **20**: 332-347, 1930.
2. Dippel, A. L. Two cases of congenital heart disease in which diagnosis was made before birth. *Am. J. Obst. & Gynec.* **27**:120-123, 1934.
3. Fenichel, N. M., and Kurzrok, L. Congenital heart disease manifesting arrhythmia in utero. *New York State J. Med.* **42**:151, 1942.
4. Roberts, J. T. Diagnosis of congenital heart disease before birth and hereditary factor in congenital heart disease. *J. Tech. Methods* **18**: 101-105, 1938.
5. Geiger, C. J., and Hines, L. E. Prenatal diagnosis of complete congenital heart block. *J. A. M. A.* **115**:2272, 1940.
6. Heubner, D. Über die Bedeutung von Herzblock bei Neugeborenen. *Ztschr. f. Kreislaufforsch.* **30**:600-602, 1938.
7. Jordan, F. C., and Randolph, H. Congenital complete heart block diagnosed in utero with sound tracings and simultaneous electrocardiograph of mother. *Am. Heart J.* **33**:109-111, 1947.
8. Ottow, B. Intrauterine Wahrscheinlichkeitsdiagnose eines Herzblocks bei der Frucht-klinisch am Neugeborenen bestätigt. *Zentralbl. f. Gynäk.* **63**:715-719, 1939.
9. Plant, R. K., and Steven, R. A. Complete AV block in fetus. *Am. Heart J.* **30**:615-618, 1944.
10. Witt, D. B. Congenital complete auriculoventricular heart block. *Am. J. Dis. Child.* **47**:380-387, 1934.
11. Yater, W. M. Congenital heart block: review of literature; report of case with incomplete heterotaxy; electrocardiogram in dextrocardia. *Am. J. Dis. Child.* **38**:112-136, 1929.
12. Kriszt, J. Angeborener sino-aurikulärer Block bei einem Neugeborenen. *Zentralbl. f. Gynäk.* **61**:2515-2518, 1937.
13. Maclellan, E. K. Double placenta praevia (binovular twins) and prenatal diagnosis of congenital heart in successive labors. *Brit. M. J.* **1**:14, 1935.
14. Phillip, E. Angeborener kindlicher Herzfehler, intrauterin wahrgenommen. *Ztschr. f. Geburtsh. u. Gynäk.* **91**:665-668, 1927.
15. White, P. D., Eustis, R. S., and Kerr, W. J. Congenital heart block. *Am. J. Dis. Child.* **22**:299-306, 1921.
16. Carr, J. G., and McClure, W. B. Auricular flutter in newly born infant. *Am. Heart J.* **6**:824-829, 1931.
17. Tarnower, H., and Lattin, B. Tachycardia in newborn. *New York State J. Med.* **42**:805-809, 1942.
18. Garvin, J. A., and Kline, E. M. Congenital paroxysmal tachycardia: report of case recognized antepartum. *Am. Heart J.* **33**:362-365, 1947.
19. Tollas, H. Über einen Fall von intrauterin festgestellter paroxysmaler Tachycardie. *Zentralbl. f. Gynäk.* **57**:60-63, 1933.
20. Blondheim, S. H. Technique of fetal electrocardiography. *Am. Heart J.* **34**:35-49, 1947.
21. Burnham, L. Unusual irregularity of fetal heart during pregnancy. *Am. J. Obst. & Gynec.* **37**:164, 1939.
22. Hubbard, J. P. Paroxysmal tachycardia and its treatment in young infants. *Am. J. Dis. Child.* **61**:687-709, 1941.

Massachusetts Physicians Art Society

10. Fishing Boats

Exhibited at Massachusetts Medical Society, 1952

Pastel by

Grantley W. Taylor, M.D.

Visiting Surgeon
Massachusetts General Hospital

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38501

PRESENTATION OF CASE

A sixty-seven-year-old woman was admitted to the hospital because of nausea, vomiting and weight loss.

The patient had felt well until seven months before entry, when she began to have frequent episodes of nausea followed by vomiting of bile-stained, recently ingested food, associated with many gaseous eructations. Vomiting occurred ten minutes to two hours after meals. These symptoms became progressively worse until she was hardly able to retain any food. During the same period she had lost 60 pounds in weight and experienced some mild left-upper-quadrant aching usually nonradiating but recently penetrating through to the interscapular area of the back. Pain was never a prominent symptom, however. She had alternating episodes of constipation and diarrhea for the several months before admission.

There was no history of hematemesis, jaundice or melena. Four years prior to entry she had an uneventful cholecystectomy for cholecystitis and cholelithiasis.

Physical examination revealed an obese woman in no acute distress. The lungs were clear. The heart was enlarged 2 cm. to the left of the midclavicular line, and a Grade 2 soft systolic murmur was heard in the aortic area and at the apex. The abdomen was obese, and there was slight direct tenderness in the midportion of the left upper quadrant. No masses were palpated.

The temperature was 99.6°F., the pulse 92, and the respirations 20. The blood pressure was 148 systolic, 80 diastolic.

The urine had a specific gravity of 1.025 and gave a + test for albumin; the sediment contained 20 white cells and frequent hyaline casts per high-power field. Examination of the blood revealed a hemoglobin of 13.6 gm. per 100 cc. and a white-cell count of 5300, with 74 per cent neutrophils, 23 per cent lymphocytes, 1 per cent monocytes and 2 per cent eosinophils. The nonprotein nitrogen was 48 mg. per 100 cc., and the sodium 134.8 milliequiv., the chloride 99 milliequiv., and the potassium 4.6 milliequiv. per liter. The prothrombin time was 13 seconds (normal, 13 seconds). A gastric analysis was guaiac negative and showed no free hydrochloric acid. On gastric aspiration 250 cc. of foamy, bile-tinged fluid was recovered. Of two gastric-fluid cytologic examinations, one was unsatisfactory, and the other doubtful. An electrocardiogram was considered to be within normal limits.

A plain x-ray film of the abdomen showed normal kidney shadows; the liver, spleen and psoas muscles were not remarkable. No urinary or biliary calculi were observed. A roentgenogram of the upper

FIGURE 1.

gastrointestinal tract showed no evidence of varices. There was a little widening of the diaphragmatic hiatus and possibly an early sliding-type hernia. The stomach rugae were very coarse. The antrum was a little narrowed, had rather heavy folds and, toward the end of the examination, had a polypoid appearance. There was no delay in the passage of barium through the stomach or large duodenal cap, which was completely smooth. The duodenal loop, which filled rather slowly, dilated to about four times its normal caliber from the pylorus to the ligament of Treitz at the angle of the stomach. In the film taken in the erect position the examiner could see a round area of gas measuring at least 4 cm. in diameter in this region before it filled with barium. The area

retained barium throughout the examination. After half an hour only traces of barium were seen in the jejunum, whereas the duodenum was dilated and filled with a mixture of fluid and barium (Fig. 1). On two films there were some negative defects in this area that were thought to lie in the colon. The diameter of the duodenal loop was not enlarged. At examination an hour and fifteen minutes later the antrum and duodenal loop had not changed in appearance, and only a small amount of barium had passed into the jejunum. At two hours, more barium had passed into the jejunum and had passed rapidly through the terminal ileum. The duodenal loop was still widened and antiperistalsis was visualized returning barium to the stomach. Several hours later the stomach still contained some barium, and the duodenal cap and loop were still dilated, although the barium column had now reached the hepatic flexure.

In the hospital there was little change in the patient's condition and on the eighth hospital day an operation was performed.

Differential Diagnosis

Dr. Milford D. Schulz*: How much did the patient weigh before she started losing weight?

Dr. Edgar B. Taft: She went from 227 to 160 pounds.

Dr. Schulz: She was not cachectic, then. Did she ever have a guaiac-positive stool?

Dr. Taft: There is no record of a guaiac test on the stool.

Dr. Schulz: I think the last statement, that on the eighth day an operation was performed, is the most important in the whole protocol, because I am sure that is the only way the diagnosis could have been made. This woman had a semichronic obstruction high in the intestine, with a more or less acute episode. Where was that obstruction, and what was its cause? The location of an obstruction can be best found by x-ray studies.

The films show a widely distended duodenum as far as the ligament of Treitz, beyond which the small bowel is not demonstrably distended (Fig. 1). I do not see the bubble of gas that is mentioned in the protocol, but I do see a collection of barium in a cavity, which is irregular in outline and is probably not a normal viscus — not the stomach or duodenum. I think the point of obstruction is in the distal duodenum near the ligament of Treitz.

What caused the obstruction? The structures in that region, in which the lesion responsible for the obstruction was located, are the duodenum, the stomach, the pancreas, the lymph nodes, the kidney and the mesocolon. What type of mischief can involve that area? Neoplasms and inflammatory conditions are among the most likely. One should examine the various possible sites for a lesion. Was it primary in the stomach? Probably not; the stomach looks fairly normal. The areas of irregularity described in the antrum were probably secondary to the chronic obstruction, which was only a short distance from the stomach. With regurgitation of bile and constant effort on the part of the stomach, I should think it would be natural to find some gastritis. There is nothing to support primary disease of the stomach.

Primary disease of the duodenum, on the other hand, was certainly present. A congenital anomaly, such as reduplication, should have been manifested long before admission to the hospital. Once in a while there is intermittent obstruction in the distal duodenum from compression of the duodenum by the overhanging superior mesenteric vessels, but that condition is not severe, is only rarely symptomatic and does not look like this on the x-ray films. A polyp in the duodenum could not explain the barium outside. Just to make sure that all the queer things are not overlooked, I shall mention a gallstone that eroded into the duodenum, became incarcerated there and thus caused obstruction; but then the fistula ought to be shown by air in the biliary tree. Primary carcinoma of the duodenum is a rare disease. It certainly could have caused the ulceration and obstructed the duodenum, with formation of a cavity outside. Although I have never seen a benign ulcer so far down in the duodenum, I suppose it could occur. Certainly, a benign peptic ulcer in the distal duodenum presents an amazing appearance — large masses of inflammatory tissue, with large ulcerations. I do not believe a foreign body can be entirely eliminated either inside or outside the duodenum. An ingested foreign body stuck in the duodenum would produce obstruction — but why, after all these months, and why should it cause ulceration? A sponge outside the duodenum, giving rise to an inflammatory reaction, may have been left in at the time of the previous cholecystectomy — perish the thought! A diverticulum of the duodenum that had become infected and ulcerated, I suppose, could also have caused an inflammatory reaction, although I have never heard of that condition. Moreover, that is an uncommon position for a diverticulum, and there were no other diverticula in the gastrointestinal tract.

The pain in the back makes one think of something in the region of the pancreas. Carcinoma of the tail of the pancreas, since the tail is near this part of the duodenum, may, I suppose, involve the duodenum and cause obstruction and ulceration; more often, it involves the stomach.

Malignant retroperitoneal tumors must be considered; I do not see how they can be eliminated. The pain in the back certainly suggests a tumor arising retroperitoneally. Lymphoma is the most likely retroperitoneal tumor. Yet I should like to see evidence of lymphoma elsewhere, such as an enlarged spleen, liver or lymph nodes. The lack of

*Radiologist, Massachusetts General Hospital.

such evidence does not necessarily mean anything; I believe most abdominal lymphomatous disease is not heralded by peripheral lymphadenopathy or mediastinal disease. The fact that the patient had not bled does not rule out carcinoma or lymphoma, although I think bleeding into the gastrointestinal tract is not an uncommon finding with lymphomatous involvement of the stomach or bowel.

I have not talked about the kidneys because the outlines were normal and no other information pointed to them. They cannot be eliminated entirely, but should not be too seriously considered without urinary symptoms.

This was a lesion obstructing the distal duodenum, with ulcerations and probably abscess formation outside the duodenum. I think lymphoma arising in the retroperitoneal area or primarily in the duodenum, and primary carcinoma of the duodenum or of the pancreas secondarily involving the duodenum, are likely possibilities. Just to be fancy, I shall mention carcinoid, although I do not know that I have ever seen a carcinoid in this portion of the small bowel. Actually, I do not know how one can make a histologic diagnosis beyond enumerating the possibilities. As I said before, the most important thing is that the patient was explored. If I must choose a single diagnosis, for no conclusive reason I shall say malignant lymphoma arising in the retroperitoneal lymph nodes and involving the duodenum secondarily.

Dr. Gordon A. Donaldson: I might give you some idea of Dr. Arthur W. Allen's thoughts before operating on this woman. She was starving to death because of the obstruction and had lost a total of 67 pounds. We did not consider any cholecystectomy complications, strangely enough. The x-ray films were taken outside the hospital by a private roentgenologist. He laid stress on the smoothness of the antrum of the stomach and believed that possibly there was involvement of the structures in that region with foreshortening of the ligament of Treitz, caused by spread of a malignant process to the ligament with obstruction as a result. This case illustrates how an initial x-ray report colors one's actions because we gave considerable thought to that and did study her gastric secretions and function. We also wondered about a superior-mesenteric-vessel compression, as Dr. Schulz mentioned, although the story was not very good for it and the obstruction was not in the right place. When we reviewed the films here, one of the roentgenologists did suggest the proper diagnosis.

Clinical Diagnoses

Carcinoma of stomach.
Obstruction of duodenum.

Dr. Schulz's Diagnosis

Malignant lymphoma of retroperitoneal lymph nodes, with secondary involvement of duodenum.

Anatomical Diagnosis

Adenocarcinoma of jejunum, with two metastases to serosa of jejunum distal to primary lesion and to one mesenteric lymph node.

Pathological Discussion

Dr. Donaldson: Dr. Allen operated on this woman. We were wrong about the site of the obstruction, although the preoperative diagnosis was not too far off. The obstruction was actually in the jejunum; the ligament of Treitz itself was perfectly free. The duodenum was greatly dilated, larger than the x-ray films lead one to believe, and the stomach was essentially normal. There was a constricting lesion in the jejunum about 10 cm. from the actual ligament of Treitz.

Dr. Taft: According to the operative note it was not far from the ligament of Treitz.

Dr. Donaldson: It was far enough along so that an anastomosis could be made.

Dr. Taft: Dr. Allen said he had to free up about 5 cm. of the duodenum to make the anastomosis.

This was a carcinoma of the jejunum just distal to the ligament of Treitz. The lesion was moderately large and cauliflower-like; it projected into the lumen of the bowel and did not constrict the bowel much as far as we could see. The proximal bowel was markedly thickened, edematous and dilated. When the operation was nearly over, the surgeons discovered two other nodules of tumor farther along in the jejunum and one lymph node that was involved with tumor in the mesentery of this portion of the jejunum. When Dr. Castleman examined these sections he believed that the jejunal tumor was probably primary since there was erosion of the mucosa and replacement by tumor; however, since so many lesions involved the bowel we could not rule out the possibility that they were all metastatic lesions from some other source. Dr. Allen had explored quite carefully and had felt nothing more. Subsequently, the patient has had no symptoms of another primary tumor so that we believe we are justified in calling this a carcinoma of the jejunum with metastases distally to the wall of the jejunum and to one of two lymph nodes.

A Physician: How far down was the second area?

Dr. Taft: The first specimen, including the main tumor, was about 60 cm. of bowel; the second piece of bowel, which was 50 to 60 cm. in length, contained the two nodules nearly in its midportion so that I should estimate that there was 70 or 80 cm. of bowel between what we considered the primary and the two lesions that were probably metastatic.

A Physician: What were the x-ray clues that suggested the diagnosis?

Dr. Donaldson: One film suggested a short segment of proximal, very dilated jejunum. The actual point of obstruction was never visualized.

I think the radiologist was making the diagnosis on the law of chances that the most likely obstruction in that region was carcinoma.

DR. TAFT: This is a rare lesion, and the diagnosis is not frequently made by x-ray examination.

CASE 38502

PRESENTATION OF CASE

A fifty-year-old woman was admitted to the hospital because of dyspnea.

One and a half years before admission the patient first noted shortness of breath on exertion and easy fatigability. This was followed by episodes of paroxysmal nocturnal dyspnea and orthopnea requiring three pillows for relief. When her physician found her to be anemic, she began taking iron and liver pills and digitalis. On this therapy her well-being increased, and the symptoms improved; however, she continued to tire easily and to have some exertional dyspnea. Six months before entry she had a febrile illness, allegedly pneumonia, which lasted for two weeks. Two weeks before entry the dyspnea and orthopnea became much worse, and the digitalis was discontinued. The dyspnea continued to become more severe until the slightest effort left her panting, sweating and worn out. Five days before admission the ankles became swollen, but the swelling disappeared a short time after she received an intramuscular injection. During the few days before admission she had several episodes of severe dyspnea during which she "fainted and passed out of the picture." Two days before admission she became nauseated and since then had been able to retain very little of what she ate or drank; she had vomited four or five times, the vomitus containing bile-stained material. For the ten days before entry she had been on a salt-free diet and had received daily "injections."

There had been no chest pain, hemoptysis, chronic cough or other gastrointestinal or urinary symptoms. Until a month before entry her appetite had been good, but her weight had decreased from 189 one and a half years before admission to 120 pounds. She had noted that she perspired very easily, that she felt more uncomfortable in hot weather and that for the last few months she had become more nervous and irritable. For three months her menstrual periods had become very scanty.

She had had severe attacks of hay fever five years previously. There were no other known serious illnesses.

Physical examination revealed a very poorly nourished woman who looked much older than her stated age and who had moderate respiratory distress while sitting upright in bed. There was no cyanosis or clubbing of the fingers. The skin was cold and somewhat dry. The neck veins were distended and pulsated slightly while she was sitting up. The thyroid gland was palpable, but did not seem to be enlarged. The chest was emphysematous, and both leaves of the diaphragm were low and only moved slightly on respiration. There were a few rales at the lung bases. The heart was enlarged, the border of dullness extending to the left. The heart sounds were faint, and no definite murmurs were heard. The pulmonic second sound was louder than the aortic. A slightly tender liver edge was palpable 4 fingerbreadths below the costal margin. There was a good-sized umbilical hernia. The spleen was not palpable. Rectal and pelvic examinations were negative. There was no peripheral edema. Neurologic examination was negative.

The temperature was 98°F., the pulse 100, and the respirations 24. The blood pressure was 114 systolic, 80 diastolic.

The urine had a specific gravity of 1.020 and was normal. Examination of the blood showed a hemoglobin of 13.0 gm. and a white-cell count of 8400, with a normal differential. The sedimentation rate was 20 mm. in one hour. The nonprotein nitrogen was 35 mg., the serum bilirubin 0.8 mg. direct and 1.7 mg. total, the serum cholesterol 166 mg., the alkaline phosphatase 11.2 units and the total protein 6.41 gm. per 100 cc., with an albumin-globulin ratio of 0.7; the sodium was 119.6 milliequiv., the chloride 96 milliequiv., the potassium 5.2 milliequiv., and the carbon dioxide 28.7 milliequiv. per liter. The prothrombin time was 15 seconds (normal, 13 seconds); the cephalin-flocculation test was ++ in twenty-four and +++ in forty-eight hours, and a bromsulfalein test showed 65 per cent retention of the dye. A basal metabolic rate was +1 per cent; the forty-eight-hour radioactive iodine uptake of the thyroid gland was 16.4 per cent, and the protein-bound iodine 7.6 gamma per 100 cc. A two-hour test for urinary urobilinogen was 2.0 Ehrlich units. A tuberculin test (1:10,000) was negative, as was a blood Hinton test. The circulation time (arm-to-tongue method) was 31 seconds. The venous pressure was equivalent to 260 mm. of water (corrected). An electrocardiogram showed sinus tachycardia at a rate of 105, with bigeminy due to ventricular premature beats, a PR interval of 0.14 and a QRS interval of 0.08 second, a tendency to right-axis deviation, low voltage and nonspecific ST-segment and T-wave changes. Roentgenograms of the chest showed the heart to be markedly enlarged, predominantly in the region of the left ventricle, with possibly some element of left-auricle enlargement. It appeared that the right ventricle might also be enlarged. The pulmonary vessels were moderately congested; fluoroscopic examination showed the cardiac pulsations to be within normal limits. A gastrointestinal series and barium-enema examination were negative. A gastric aspiration showed free hydrochloric acid.

The patient responded poorly to digitalis and diuretics. Shortly after admission she experienced

a slight muscular ache with tenderness in the left calf and then a cough with some blood-tinged sputum, accentuation of the dyspnea and transient, mild pain in the anterior part of the chest. The temperature ranged from 100 to 102°F., and the pulse was 100 and regular. An electrocardiogram showed no definite change, and examination of the chest was negative. A roentgenogram of the chest demonstrated a small amount of fluid in the left costophrenic angle, congestion of the pulmonary vessels and a small area of increased density overlying the left-lower-lung field just adjacent to the left border of the heart (Fig. 1).

On the fifteenth day a bilateral common-femoral-vein ligation was performed; no clots were found.

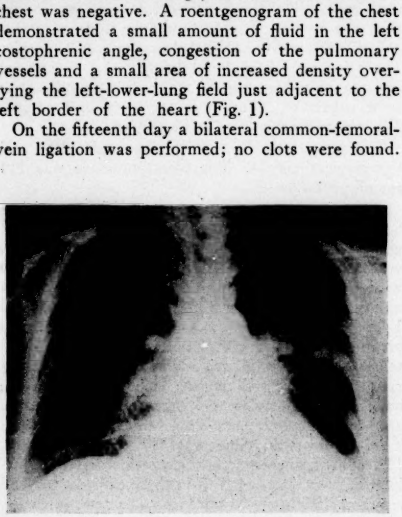


FIGURE 1.

Dicumarol was started, and an adequate therapeutic prothrombin level maintained. She continued to have a low-grade temperature elevation (between 99 and 101°F.) and a cough productive of much sputum, which was occasionally blood tinged. Blood cultures and agglutination tests for brucellosis and typhoid fever were negative. On the nineteenth day an x-ray film of the chest demonstrated a rather discrete density in the left upper lobe; the nonprotein nitrogen was 50 mg. per 100 cc., and the sodium 125.0 milliequiv. and the potassium 5.9 milliequiv. per liter. The patient seemed to improve somewhat but continued to be apathetic and weak, and showed persistent venous engorgement. On the twenty-ninth day it was noted that the cardiac rhythm was totally irregular; an electrocardiogram showed a sinus tachycardia at a rate of 120, with multiple premature beats and short runs of bigeminy and trigeminy. She began to have periods of severe dyspnea, lasting up to several hours, which were most often precipitated by heat and nervousness and relieved somewhat by aminophylline. During these episodes the lungs were clear; there was no cyanosis, chest pain or change in pulse. X-ray films of the chest showed no significant change. On the thirty-ninth day extreme dyspnea with cyanosis of the lips and nail beds developed; examination showed cold, clammy extremities, nonpulsating, slightly distended neck veins and clear lungs. The liver edge was palpable 4 fingerbreadths below the costal margin. The pulse was 90, and the respirations 60. The blood pressure was 80 systolic, 60 diastolic. A few hours later the blood pressure was unobtainable, the pulse 150 to 160, and the respirations 50 to 60. She became progressively more cyanotic in spite of oxygen therapy, finally became comatose about twelve hours after the beginning of this episode and died one hour later. Five hours before death an electrocardiogram showed disintegration of the heart action, with an irregular ventricular rate around 150 and runs of ventricular flutter; the QRS segment was indistinct, varying in configuration from beat to beat. No definite auricular activity was seen.

DIFFERENTIAL DIAGNOSIS

DR. CONGER WILLIAMS*: May I see the x-ray films?

DR. JAMES J. MCCORT: The films made on admission show the heart to be grossly enlarged, the border extending to the left. This could be due to either enlargement of the left ventricle or displacement to the left by enlargement of the right ventricle. On the basis of the lateral film, one wonders if both ventricles were not enlarged. In addition, there is elevation of the left main bronchus, suggesting enlargement of the left auricle posteriorly. The major branches of the pulmonary arteries are prominent and slightly dilated. The aorta shows only slight tortuosity.

A film of the chest taken two weeks later shows no significant change and confirms the previous impression of enlargement to the left, with displacement of the barium-filled esophagus posteriorly by an enlarged left auricle.

The film of the chest made one day after the acute episode of pain in the left side of the chest (Fig. 1) demonstrates a rather large area of increased density in the inferior lingular segment of the left upper lobe and a smaller area of increased density at the right base and also at the left base, with fluid blunting the costophrenic sinuses. Two weeks later the area of increased density in the left upper lobe and the small amount of fluid at the left base are still present. No new areas of infarction are seen, and the size and configuration of the heart are unchanged.

DR. WILLIAMS: It seems obvious that this patient suffered from heart disease and that she also had pulmonary involvement and probably hepatic involvement other than that to be expected as a consequence of the heart failure. The difficulty

*Associate physician, Massachusetts General Hospital.

here comes in assessing the interrelation of these factors and deciding on one or several etiologies to explain the series of events. On first reading this protocol I was struck by the apparent lack of cause for what seemed to be heart failure. None of the usual factors seen in a patient of this age — namely, coronary-artery disease with old infarction, hypertension, valvular disease or persistent arrhythmia — were present as far as I can judge from the evidence. Of course, it is possible that one of these factors such as hypertension was present before the patient came into the hospital and disappeared as the result of the acute illness; if that was so, I have no way of proving it and shall simply suspect the possibility. The evidence of cardiac involvement includes definite cardiac enlargement, faint heart sounds, elevation of peripheral venous pressure that was measured as equivalent to 250 mm. of water and hepatic engorgement, which probably goes with the high level of venous pressure. It seems to me that I can explain this sequence of events, which started a year and a half before death, by assuming that she had some destructive cardiac lesion involving either the left ventricle alone, at first, or the heart as a whole. There are many processes to consider, the first of which is disease involving the myocardium and at the same time producing a general systemic upheaval to account for the weight loss and loss of nutrition.

In the group of diseases that may involve other parts of the body as well as the heart is thyrotoxicosis. It should be remembered that the patient's appetite had not been good for a month before entry, her weight had decreased almost 60 pounds, and she had perspired easily and had more discomfort in hot weather. The Service apparently also thought thyrotoxicosis was possible; she had a good work-up, including radioactive iodine uptake, basal metabolic rate and protein-bound-iodine level. The low iodine uptake of 16 per cent could be accounted for by previous iodine taken inadvertently in food or medicine. The fact that the uptake was low does not necessarily rule out thyrotoxicosis. The normal blood iodine level is against thyrotoxicosis. The basal metabolic rate I shall throw out because too many other factors may alter it. For all those reasons, I doubt very much whether she had thyrotoxicosis.

Another disease that involves the myocardium as well as the other organs in the body is polyarteritis; however, evidence of renal involvement was not convincing, nor was there peripheral neuritis, which commonly occurs with polyarteritis. Another such disease is lupus erythematosus. This patient was somewhat old for that. She had no other evidence to support such a diagnosis: no obvious renal involvement and no suggestive blood picture. Scleroderma, another of the so-called group diseases, may involve the heart and other viscera, particularly the upper gastrointestinal tract. There were no changes in the skin.

Another disease that will do this is hemochromatosis. In this hospital I believe we have had 1 patient with hemochromatosis involving the myocardium. One point that rules this out almost completely is the sex of the patient. The incidence of female to male patients affected by this disease is 1:10 or less. She had none of the other findings — pigmentation of the skin, diabetes and so on.

Among the other possibilities is primary amyloidosis. Although that remains a possibility, none of the other muscles in the upper gastrointestinal tract, the larynx, the tongue and so on were involved. Primary amyloidosis would not explain the liver involvement except as secondary to congestive heart failure. In sarcoidosis, too, there may be definite myocardial involvement, even congestive failure, liver enlargement and so on. Again, I have nothing on which to base such a diagnosis. Certainly, the changes in the lungs do not suggest it.

Another possibility to be considered is that of myocarditis from infection. This patient had an illness diagnosed as pneumonia before she came into the hospital; however, dyspnea began before the episode of so-called pneumonia. Although the long duration of the illness, a year and a half, is against myocarditis from some unknown etiologic agent such as a virus, that remains a possibility.

Several disorders of unknown etiology involving the myocardium have been grouped together and called isolated myocarditis or Fiedler's myocarditis. It is possible that this patient had one of the so-called "isolated" myocardial lesions. Occasionally, such a process will continue for a year or more before death finally results.

In addition to cardiac involvement this patient probably had pulmonary embolism; the evidence in favor of that is good. She had paroxysms of dyspnea not always explained by exertion or position in bed, and several rises in temperature. The x-ray evidence was quite consistent, as was the pain in one leg and so on. Certainly, the terminal episode suggested pulmonary embolism more than anything else. Obviously, the Service thought she had pulmonary embolism and had the leg veins tied. The fact that no clots were found on ligation means nothing; she may well have had phlebothrombosis to account for the episode of pulmonary embolism. It is also possible that pulmonary emboli came from the ventricular wall. Myocarditis, especially the so-called isolated myocarditis, produces roughening of the endocardial surface and thus predisposes to mural-thrombus formation. Emboli on both sides — both to the pulmonary circuit and to the peripheral circuit — are fairly common in such conditions. She probably had pulmonary embolism from one of those sources and possibly from a third source, the right auricle. Although she had an

arrhythmia, I do not know for sure that she ever had auricular fibrillation.

The liver-function tests suggested hepatic involvement. It is possible, in view of the known high venous pressure that most of those findings, the positive cephalin-flocculation test, the slight increase in bilirubin and so on, can be explained by the effect of the increased venous pressure on the liver. The one finding that is slightly unusual is the 65 per cent bromsulfalein retention. Ordinarily, one does not see that much alteration in this test purely from congestive phenomena; it is possible that fairly severe changes in liver function and architecture had taken place as a result of the long-continuing, high venous pressure. I must also think of the possibility of constrictive pericarditis. The history, first dyspnea and then increase in peripheral venous pressure, was not the usual one. Of course, the symptoms depend on the site of constriction. With no other findings to point to that diagnosis I have abandoned it.

My final opinion is that this was progressive myocarditis, perhaps one of the isolated myocarditides, complicated by pulmonary embolism either from mural thrombi or from the legs. One other possibility I should mention before I close is that this whole picture was based on pulmonary disease with a secondary cardiac process — namely, cor pulmonale — complicated by more acute episodes due to emboli. Yet, from the x-ray films, I would be more inclined to suspect myocardial involvement.

Dr. Mark D. Altschule: We all believed that the patient's terminal illness and some of the earlier acute episodes were caused by pulmonary emboli, but we were very much in the dark concerning the source of the emboli. We were troubled also that the response to the usual therapy was a poor one as evidenced by the fact that she died after so short a time on the ward. Among the etiologies that we considered, since there was no evidence of hypertension or coronary sclerosis, were some form of myocarditis and primary pulmonary hypertension of unknown origin. We had no way of establishing the likelihood of either one, and therefore they were both speculations.

Dr. John T. Stanbury: We were completely puzzled about the nature of the disease and considered what other procedures we could do to establish the diagnosis. There seemed to be nothing else we could do, so we made the diagnosis of nonspecific or undiagnosable inflammatory myocarditis.

Dr. Kurt J. Isselbacher: Is idiopathic hypertrophy included in the group of so-called isolated myocarditis, Dr. Williams?

Dr. Williams: I do not believe I can make that diagnosis. I think that would be the most unsatisfactory of all the diagnoses.

Dr. Isselbacher: Is there not a familial tendency that sets it apart from the others?

Dr. Williams: I believe such cases have been described; I have no way of making such a diagnosis here.

Dr. Benjamin Castleman: The diagnoses made by the group of 11 fourth-year students who discussed this case before the conference were: tumor, 5; amyloidosis, 2; and some form of heart disease, 4. The heart diseases considered were arteriosclerotic disease, collagen disease and endocardial fibrosis.

Dr. Williams: Did they consider that the congestive heart failure was on the basis of tamponade produced by tumor?

Dr. Stanbury: The diagnosis of tumor was seriously entertained during life because the patient had lost a great deal of weight. We wondered if she might have had a carcinoma of the pancreas that had metastasized to the liver and elsewhere.

Clinical Diagnoses

Cor pulmonale.
Multiple pulmonary emboli.
Arteriosclerotic heart disease.

Dr. Williams' Diagnoses

Progressive myocarditis, ?isolated.
Multiple pulmonary emboli.
Cardiac mural thrombi.

Anatomical Diagnoses

Idiopathic cardiac dilatation and hypertrophy.
Endocardial fibrosis.
Mural thrombi, right auricle and both ventricles.
Pulmonary infarcts.

Pathological Discussion

Dr. Castleman: The heart was enlarged mostly because of dilatation, although there was some hypertrophy. The dilatation involved both sides of the heart, but was greater on the right. The endocardium of the left ventricle was thicker and whiter than that on the right. The left auricle was not much enlarged. There was no disease of any of the valves. There were large numbers of mural thrombi in the right ventricle, and some at the apex. At the apex of the left ventricle there was another thrombus. A large mural thrombus in the right auricle was probably the source of the emboli to the lungs, in which there were two large infarcts as shown by x-ray examination. Although the emboli may have come from the right ventricle, the thrombi were so much larger and more friable in the auricle that I believe the emboli came from the right auricle. The left circumflex coronary artery was moderately narrowed with atheroma, but the other coronary arteries were normal.

Many sections of the myocardium showed no evidence of myocarditis, but there was a great deal of endocardial and subendocardial thickening. The etiology of subendocardial fibrosis is still unsettled. Some physicians believe the endocardial

thickening has something to do with the stasis of blood in the ventricle. That may be true with heart failure of any sort, but usually the thickening is slight. We have seen this endocardial fibrosis so often in cases that were called idiopathic hypertrophy or myocarditis that we think there must be some connection. Dr. Thomas has been reviewing our cases of this condition. Perhaps he will say a word about them.

Dr. Wilbur A. Thomas: We occasionally see a situation somewhat similar to this in infants dying with evidence of cardiac dysfunction. These infants usually show markedly dilated and hypertrophied hearts, with tremendous thickening of the endocardium of one or more chambers. Often, but not always, there is involvement of one or more valves by the endocardial overgrowth, with distortion and interference with function. Histologically, in typical cases, this thickened endocardium is seen to be composed of somewhat primitive connective tissue, with striking proliferation of elastic fibers. We have considered the hypothesis that some of the cases in adults, such as the one under discussion, are a mild form of the same condition in which symptoms have been delayed because of the ability of the heart to compensate. Elastic-tissue stains on this endocardium and on similar cases in our files do show marked proliferation of the elastic fibers, and the appearance is thus consistent with an adult form of infantile fibroelastosis. On the other hand, the elastic tissue, regardless of the etiology of the endocardial thickening, would probably be increased since it is likely to develop in any proliferating tissue subjected to alternate stretching and relaxation.

Dr. Castleman: I do not believe that the amount of coronary-artery disease that this patient had could account for this thickening, or if so, that the fibrosis would be localized to the endocardium. There was no fibrosis of the myocardium below that area.

Dr. Williams: How many of these cases show no involvement of the valves? Is that not rather usual?

Dr. Castleman: No; the valves are not usually involved.

We are left with a diagnosis of dilatation of the heart associated with perhaps slight hypertrophy — the left ventricle is about normal. The x-ray shadow was due to the marked dilatation. Some people have entertained the idea that this condition may be a deficiency disease — beriberi heart disease with heart failure — leading to stasis in the ventricle and the production of the fibrosis.

Dr. Stanbury: Hasn't that been described frequently in Africa?

Dr. Thomas: Dr. Davies,* a pathologist in Uganda, East Africa, has described a condition in malnourished natives that seems to be similar in some respects to our cases. Clinically, they showed the signs of severe congestive heart failure without response to any form of therapy, including vitamins. At autopsy the hearts were not hypertrophied but demonstrated varying degrees of endocardial and subendocardial fibrosis. In addition, he noted striking hydropic degeneration of the adjacent myocardial fibers without appreciable inflammatory reaction. He considers this degeneration of the muscle fibers the basic disease and regards the thickening of the endocardium as due to replacement fibrosis of necrotic subendocardial muscle; he calls the disease subendocardial necrosis.

I have not been impressed with this change in the majority of our cases. In most, including the case under discussion, the underlying myocardium is unremarkable. A few of our cases do show a slight degree of vacuolation similar to that described by Davies, but I have been inclined to discount its significance in our cases since similar, slight changes are not infrequently seen in routine autopsies.

Dr. Stanbury: We had another patient, a young woman, on the ward at the same time on whom we thought we could make a flat-footed diagnosis of subendocardial fibrosis; we did not dare to make that diagnosis twice. That patient, who had a large heart, was having arterial emboli without any obvious source other than the heart.

Dr. Castleman: This patient also had arterial emboli that went to the spleen. The liver showed marked central congestion with a great deal of necrosis, which would account for the liver findings.

The right ventricle was not hypertrophied. We cannot call this a cor pulmonale. Although some pulmonary arteries showed evidence of old embolization, it was not sufficient to produce a pulmonary hypertension.

*Davies, J. N. P. Pathology of Central African natives. Mulago Hospital post-mortem studies. IX. Cardiovascular disease. *East African. M. J.* 25:454-467, 1948.

The New England Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. — Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. — Richard E. Alt, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. — Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR
James F. Ballard, BOOK REVIEW EDITOR
Milton C. Paige, Jr., BUSINESS MANAGER

EDITORIAL BOARD
C. Guy Lane, M.D. — Vernon P. Williams, M.D.
Henry R. Viets, M.D. — Benjamin Castleman, M.D.
Robert M. Green, M.D. — Hugh R. Levell, M.D.
Dwight O'Hara, M.D. — J. Englebert Dunphy, M.D.
Fletcher H. Colby, M.D. — Robert W. Buck, M.D.
Robert L. Goodale, M.D. — Herrman L. Blumgart, M.D.
Chester M. Jones, M.D. — Frank N. Allan, M.D.
Harvey R. Morrison, M.D. — Harvey A. Kelly, M.D.
Maxwell Finland, M.D. — Langdon Parsons, M.D.
Deering G. Smith, M.D.*

*Representing the New Hampshire Medical Society.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (medical students and first-year interns, $5.00 per year); Canada, $9.0 per year (Boston funds); foreign, $10.50 per year.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

BURNING TRUTHS AND BLAZING ISSUES

MAN, through the processes of an intelligence for which, imperfect as it is, he can hardly be held responsible, has created for himself a world of burning issues, of blazing truths and of smoldering half truths — of causes won and lost, and of new hopes rising from the ashes of the old. For men's minds are most happily active when they have a line to which to hew.

The main recourse of a dictator, however petty, is that he must always hew to the line as he himself has drawn it, regardless of the principles of right and wrong, and so it is with the supporters of causes, high and low, that once the mind is made up any subsequent opening of it introduces the unpleasant prospect of uncertainty. It is easier to keep the mind closed than to have to adjust it eternally to new ideas — and the open mind is, moreover, inevitably subject to the suspicion of vacillation and uncertainty and even disloyalty.

There are, of course, certain axiomatic rules of conduct on which all, or nearly all, men will agree. Theft, mayhem, adultery and murder are unacceptable in most societies and under most conditions. Kindness, honesty, consideration of the rights of others and abstention from arson are believed with an almost equal intensity to be virtues, by and large. But these are not issues; they are not truly points of debate, for most persons in most places now believe in them. It must be admitted that even apparently basic principles of right and wrong were not always and everywhere accepted as such. Human bondage was a burning issue in this country almost within the memory of living man and at a time when other countries, despite their sometime favoring of the Rebel cause, professed to abhor it. It is still considered not unmannerly, in certain sections of the world, to bop one's neighbor on the head if pleasure or profit can thereby be derived.

The industrious hewing to a line, like the hue and cry of certain types of contentious editorial writing, impressive as it is, may also be one of the early steps toward a totalitarian point of view; too great a zeal in one's efforts at the control of others' thoughts betrays not only a mind that may be closed, but one that is trying to close other minds as well. Neither Republicans nor Democrats have a monopoly of all the political virtues or are cursed with all the political vices; there is still much that can be said on both sides of many questions.

A liberal thinker is not necessarily a raging Red, regardless of who may be drawn to persecute him as such, nor does every radical necessarily want to tear down the structure of his country's government by force. Even in our own learned profession it must be accepted as a first truth that the answers to such problems as those of general practice in respect to specialism and to the public, the public relations of the profession as a whole, hospital and professional relations, the functions of organized public health, prepayment for medical care, group

practice (in a nice way) and the boundaries of so-called socialized medicine, a clear definition of which is even yet lacking — these answers will come one by one. Nor will the best answers be found by any closing of the mind against any arguments that may be brought to bear on either side of any question.

The recognition of more than one point of view may be not so much a sign of weakness as of tempered judgment. More and more it seems justified to believe that the highest function of the editorial writer is to speak on controversial subjects not even with delegated authority, but to present the different points of view in the truest light possible and allow the reader to make his own decisions. For the making up of one's own enlightened mind leads to stronger convictions than the acceptance of any ready-made opinion. This is a principle often violated through ignorance, confusion, conceit and the mere acceptance of authority, for "The ox knoweth his owner, and the ass his master's crib." It has been violated, undoubtedly, in these pages, but it remains a goal toward which to work.

All who desire freedom of action — and who does not? — must remember that it has its roots in freedom of thought and of expression, and that in searching for the truth they can come closest to that freedom. Such liberty can hardly be appreciated in this country, for to no one is freedom more precious than to him who has lost it.

PERIODIC REGISTRATION OF PHYSICIANS

House Document No. 158, which has recently been filed by the Commissioner of Administration for the Commonwealth of Massachusetts as an administrative bill, brings to a head a matter that has had the attention of the Massachusetts Medical Society on many occasions during the past fifteen years. It provides simply that every registered physician shall annually, before April 1, re-register and pay a fee of $5 to the Board of Registration in Medicine.

A companion document, No. 157, seeks to increase the annual registration fee of dentists from $2 to $5. Since chiropodists, veterinarians, and embalmers register annually, paying $5 for registration and annual renewal (a pharmacist's annual registration fee is $10), it appears that House documents No. 157 and 158 have a reasonable basis, if only that of equalizing what to some may have appeared as unfair discrimination.

It is interesting that the majority of physicians who have had an active say in the Society's deliberations over the problem favored the concept of annual registration but did not believe that it was up to the Society to sponsor legislation to that effect, if, indeed, legislation were needed.

That there is no complete listing of physicians now practicing in Massachusetts has been demonstrated many times over. Lack of such a list has handicapped those planning for civil defense as well as those compiling facts and figures on the availability and distribution of physicians in the Commonwealth. It seems desirable at present, when the possible needs of civil defense are paramount, for the Massachusetts Medical Society to offer its assistance in drafting a bill that would accomplish the purposes of the Commissioner of Administration and that would make annual registration of physicians as painless a duty as possible.

THE ROCKEFELLER FOUNDATION: A TWO-YEAR REPORT

Even at midcentury many are not satisfied that those engaged in the study of human behavior and relations are genuine scientists — in other words, that the social scientists are scientists. According to a soliloquy, for an annual report is nearly always an administrative soliloquy, of Mr. Chester I. Barnard, the retiring president of the Rockefeller Foundation,* it is even questioned by some whether a substantial body of knowledge exists that can at present be distinguished as "social science."

A scientist is defined as one who attempts to obtain knowledge by observation or experiment or both, with a high degree of detachment or objectivity, his observations being susceptible at least in principle to scrutiny or repetition by others under similar conditions. He advances and tests hypotheses for this purpose, and when the data are sufficient he tries to construct theories, consistent with the data, that promote the further acquisition of knowledge and facilitate communication on his

*Barnard, C. I. *Review for 1950 and 1951*. 123 pp. New York: The Rockefeller Foundation, 1952. P. 63.

subject. Judged by the above criteria, many workers in fields of human behavior and human relations qualify as scientists according to Mr. Barnard. Doubt is expressed, however, whether there is sufficient knowledge in the field under consideration to satisfy the criteria that distinguish a science from an art or one of the humanities — namely, interconnected and self-consistent knowledge, validated by a relevant group of fellow scientists and integrated by a theory or theories accepted by most contemporary scientists as a useful expression of knowledge. This does not mean that today's theory may not be greatly modified tomorrow.

There is, however, little doubt in Mr. Barnard's mind that there are disciplined and contemplative persons who are actively applying the scientific method with increasing frequency to problems that, even when they cannot be classified as scientific, may yet come under that category given time and systematic analysis. The progress in the past decade allows confidence that finds official expression in Mr. Barnard's review for 1950 and 1951, and encourages the Rockefeller Foundation in its role of being "an experimenter in trying out new knowledge and sponsoring new methods in research and education." Mr. Barnard appears to have found it as exciting to be contemplating the thresholds of potentially new sciences as it must have been for the princes and patrons of yesteryear to watch and aid the Galileos, the Robert Boyles and the Robert Kochs in the infant fields of physics, chemistry and bacteriology. Barnard's own stewardship comes to its conclusion, but not the task of the Foundation, which, like royal patrons of old, stands ready to fit out ships for likely adventures just over the horizon.

The great Foundation, in its role of an experimenter, will continue to lend its support to pioneers as well as to members of the established professions:

> Between any science and its application to human purpose, that is, its utilization for the realizing of values there impinge alternative values and interests, invention, organization, management, regulation, patents and other factors, which have to be harmonized and integrated — a matter frequently of great difficulty even when serious conflicts of interest and controversy are not especially important, as in much engineering. The possible important difference between application of a social science and of a natural science may be that controversial attack in the former case is likely to be against the science itself or its formulated theories, whereas in the case of a natural science the attack more exclusively will be on the *means* of application rather than on the science itself.

HELPING THE HANDICAPPED

ELSEWHERE in this issue of the *Journal* a letter from the executive director of a characteristically Boston institution — Community Workshops — calls attention to its diamond jubilee. Originating in a metropolitan area noted for its number and variety of philanthropic enterprises, Community Workshops is typical of many agencies that have similarly stood the test of time, having been established in 1877 to help handicapped persons help themselves.

To give substance to Community Workshops' claim of unique service the record of a single year may be cited. In it the organization gave service to 554 persons; the end result was a return to sheltered employment in some cases, but to regular employment in industry in the majority. During the same period the Business Department sold orders totaling nearly $36,000, representing more than 39,000 articles manufactured in the Vocational Training Shop. Over 1000 additional items were produced in the Sheltered Shop and in "Homebound" programs.

Physicians of Greater Boston — many of whom may at one time or another find these services invaluable to selected patients — are reminded that vocational rehabilitation, despite the prominence that it has achieved in recent years, is not new; Community Workshops has been quietly performing similar functions for three quarters of a century.

There is a prodigious amount of quackery conducted under the guise of a strong sense of duty, which compels certain physicians to disengage themselves from the trammels of society discipline, and strike out an independent course of their own.

Boston M. & S. J., *December 15, 1852*

CORRESPONDENCE

COMMUNITY WORKSHOPS

To the Editor: May I call your attention to the importance of 1952 to Greater Boston's only Red Feather Vocational Rehabilitation Center. Seventy-five years ago the Community Workshops was incorporated to serve handicapped women of Boston. Since then, the agency has grown in service and scope.

Whereas its original program provided home sewing to women of the North End, we are now providing rehabilitation through vocational training to men and women from the entire Greater Boston area. Our program is the important next step after physical restoration has been accomplished by the physician.

At the Community Workshops a handicapped person is provided the opportunity of working with other disabled people on real work projects. Our programs are geared from simple repetitive processes for the seriously disabled to those demanding seven and a half hours of production, five days a week. In this way we are equipped to serve most types of handicaps at varying levels of work tolerance and ability.

Our training programs include garment manufacturing, office procedures, woodworking and mechanical assembly. In addition, we operate a sheltered shop for people who are so disabled that industrial employment is unlikely. Although sheltered employment is extremely important, the training program is of major concern to physicians.

We earnestly invite inquiries about our work and closer co-operation with the physicians of Greater Boston.

ESTHER C. WALTHER
Executive Director

Community Workshops
Boston

BOOK REVIEW

Psychosomatic Gynecology. Including Problems of Obstetrical Care. By William S. Kroger, M.D., and S. Charles Freed, M.D., 8°, cloth, 503 pp. Philadelphia: W. B. Saunders Company, 1951. $8.00.

The concept of psychosomatic medicine is as old as Galen, but, like some of his other advanced ideas, it had lapsed into abeyance and oblivion for many centuries. After the sensational advances in the field of psychiatry due to the work of Pinel and Freud, the early twentieth century saw a reawakening to the essential importance of the psychic factors of many somatic diseases. Particularly and most recently has this been true in the field of gynecology and obstetrics, in which the sex aspects afford prolific opportunity for psychic influence on physical diseases and functions.

The present volume, written jointly by a distinguished gynecologist and obstetrician and a well known psychiatrist, is the latest evidence of this newly-awakened interest. After a gynecologic foreword by Dr. J. P. Greenhill and a psychiatric foreword by Dr. Flanders Dunbar, who emphasizes particularly the aspects of her special field of psychology, the text presents a systematic and thorough survey of the entire subject of the correlations and interactions of psychic and somatic factors in the genesis, symptomatology, diagnosis and treatment of gynecologic and obstetric problems.

There is a consecutive and continuous consideration of the psychosomatic aspects of fetus and infant, of the mother during pregnancy, of neuroendocrinology and of some common psychosomatic problems, such as sterility, frigidity and dyspareunia. Of special interest and merit are the chapters on psychogenic therapy, on contraception, on abortion, on hyperemesis, on lactation and on hypnosis in labor. An admirable chapter on the psychosomatic aspects of pregnancy is contributed by Dr. Grantly Dick Read, of Johannesburg, South Africa.

This volume is without the routine pictorial illustration customary in such works, but by its nature it does not suffer from this omission. There is an abundance of well selected references to the literature in connection with each chapter, altogether over 1250 titles. The book is dedicated to Dr. Beltran P. Morales, who collaborated in its preparation. It is an important contribution to a less familiar field of psychosomatic medicine, from which emerges the fundamental fact that all disease has psychogenic as well as pathogenic causes.

ROBERT M. GREEN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Post-graduate Lectures on Orthopedic Diagnosis and Indications. By Arthur Steindler, M.D., professor of orthopedic surgery, State University of Iowa, College of Medicine, Iowa City, Iowa. Vol. III, Section A: *Tuberculosis of the skeletal system;* Section B: *Osteomyelitis.* 4°, cloth, 281 pp., with 255 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $8.75.

In this series of lectures Dr. Steindler thoroughly covers the subject of tuberculosis of the skeletal system, including the pathology, clinical pathology and diagnosis, prognosis and treatment, and specifically of the spine, hips, knee, foot and ankle, and of the upper extremity. The section on osteomyelitis discusses the pathogenesis, pathology and clinical pathology of the acute and chronic forms of the disease, and treatment of both types. The other lectures have to do with osteomyelitis of the spine and pelvis, and unusual forms including typhoid, Malta fever, Salmonella, smallpox and mycotic osteomyelitis and echinococcus infection of the bone. Short lists of references are appended to the chapters, and there are indexes of subjects and authors. The series should be in all medical libraries and available to all surgeons interested in diseases of the bones and joints.

Anatomy for Artists. By Diana Stanley. 8°, cloth, 108 pp., with 62 illustrations. New York: Pitman Publishing Corporation, 1952. $3.75.

Art anatomy has a long history, dating back to Dürer and his famous book on the proportions of the human body (1528) and William Rimmer, of Boston, *Art anatomy* (1854), issued in fifty copies, and others. There are a number of modern books and this latest by Miss Stanley, an artist with considerable experience in teaching life drawing, should be in collections on the subject. The text is divided into four sections: the trunk, the head and neck, and the upper and lower extremities. The illustrations are excellent.

Das Klapp'sche Kriechverfahren. By Dozent Dr. Bernhard Klapp. With the collaboration of Ella Biederbeck and Ingeborg Hess, instructors, der Schule für Krankengymnastinnen, Chirurgischen Universitätsklinik, Marburg (Lahn). 8°, paper, 70 pp., with 115 illustrations. Stuttgart: Georg Thieme, 1952. Karton. DM. 11.70. Distributed by Grune and Stratton, New York.

This monograph describes the author's method for promoting creeping in disabled persons. Biederbeck and Hess describe the technical procedures and the apparatus used in training.

Atlas of Tumor Pathology. Prepared at the Armed Forces Institute of Pathology, under the Auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council. 4°, paper, Washington, AFIP, 1951–1952.

Section II, Fascicle 6: *Tumors of the Peripheral Nervous System.* By Arthur P. Stout, M.D., professor of surgery, Columbia University, College of Physicians and Surgeons. 55 pp., 56 illustrations. 60c. Section III, Fascicle 9: *Teratomas.* By Rupert A. Willis, D. Sc., M.D., F.R.C.P., professor of pathology, University of Leeds Medical School, Leeds, England. 58 pp., 45 illustrations. 50c. Section IV, Fascicle 16: *Tumors of the Carotid Body and Related Structures (Chemoreceptor system).* By Philip M. LeCompte, M.D., and instructor in pathology, Harvard Medical School, and pathologist, Faulkner Hospital, Boston. 40 pp., 23 illustrations. 45c. Section V, Fascicle 18: *Tumors of the Mediastinum.* By Hans G. Schlumberger, M.D., professor of pathology, Ohio State University College of Medicine. 88 pp., 75 illustrations. 75c. Section VIII, Fascicle 29: *Tumors of the Adrenal.* By Howard T. Karsner, M.D., medical research advisor, Bureau of Medicine and Surgery, United States Navy. 60 pp., 47 illustrations. $1.00. Section IX, Fascicle 34: *Tumors of the Breast.* By Fred W. Stewart, M.D., professor of pathology, Cornell University Medical College, pathologist, Memorial Hospital, and attending pathologist, New York Hospital. 114 pp., 68 illustrations. $1.10.

Six parts of this projected atlas have been published, dealing with tumors of the peripheral nervous system, of the carotid body, mediastinum, the adrenal body and the breast, as well as teratomas. The plates are excellent, and there is a small amount of descriptive text. The atlas should be in all collections on pathology and on tumors.

The Yearbook of Psychoanalysis, Volume 7, 1951. Managing editor, Sandor Lorand, M.S. 8°, cloth, 271 pp. New York: International Universities Press, 1952. $7.50.

This volume in an important series contains twenty-one articles on varying aspects of psychoanalysis. An appendix presents a complete list of the contents of the six previous volumes.

Übungsheft für das autogene Training. By Professor J. H. Schultz. Sixth edition. 8°, paper, 28 pp. Stuttgart: Georg Thieme, 1952. Karton. DM 3. Distributed by Grune and Stratton, New York.

This small condensation is based on the author's larger book, *Das autogene Training*, seventh edition, Stuttgart, 1951.

Any Questions? A selection of questions and answers published in the British Medical Journal. First series. 12°, cloth, 240 pp. New York: Grune and Stratton, 1951. $2.50.

This small book was first published in London and is now issued under an American imprint. The text consists of answers to various questions on clinical subjects sent to the *British Medical Journal*.

Die Grenzen der Psychotherapie. By G. Ewald. 8°, paper, 35 pp. Stuttgart: Georg Thieme, 1952. Kart. DM 3.30. Distributed by Grune and Stratton, New York.

Dr. Ewald presents a survey of developments in psychotherapy during the last ten years.

Case Histories in Psychosomatic Medicine. By the staff of the Psychiatric Service, Massachusetts General Hospital. Edited by Henry H. W. Miles, M.D., Stanley Cobb, M.D., and Harley C. Shands, M.D. 8°, cloth, 306 pp. New York: W. W. Norton and Company, 1952. $4.50.

The material for this book was derived from the clinical conferences conducted at the hospital by members of the psychiatric staff, physicians from other services and fourth-year students at Harvard Medical School. Twenty-one cases are considered, having been selected to bring out certain aspects that may be instructive and useful to students, general practitioners and specialists. Almost all the cases have previously been published in various medical periodicals, but are brought together in one volume for the sake of convenience.

Psychiatrie Heute. By Kurt Schneider, Professor, Universität Heidelberg. 8°, paper, 31 pp. Stuttgart: Georg Thieme, 1952. Karton. DM 2.85. Distributed by Grune and Stratton, New York.

This lecture on the present status of psychiatry was delivered on November 22, 1951, at the five hundred and fifty-sixth celebration of the Ruprecht-Karl-Universität at Heidelberg.

Grundlagen der Strahlentherapie: Physik, Biologie und allgemeine Therapie. By Dr. Med. Richard K. Kepp, professor of obstetrics and gynecology, Universität Göttingen. With a foreword by Prof. Dr. Heinrich Martius, director, Universitäts-Frauenklinik Göttingen. 8°, cloth, 357 pp., with 134 illustrations. Stuttgart: Georg Thieme, 1952. Ganzleinen. DM 38.– Distributed by Grune and Stratton, New York.

This new book on "ray" therapy is well arranged and discusses in detail the physics, biology and therapeutic use of x-rays and radioactive rays and is based on a survey of the modern literature. The text is divided into three main categories: physics; biology and general therapy; and bibliography. Under physics the technical details of the various rays, including the cathode, proton and neutron, are discussed. The second part includes biology of the rays in general, their action upon cell and tissue and upon the various organs and structures of the body, the action of ionized rays, methods of protection and a long chapter on the treatment of malignant tumors. The bibliography is comprehensive in scope, comprising thirty-one pages. There is a good index. The book should be in all collections on radiotherapy and tumors.

NOTICES

NEW ENGLAND PATHOLOGICAL SOCIETY

A meeting of the New England Pathological Society will be held at Harvard Medical School on Thursday, December 18. The meeting, which will begin at 4 p.m., will be devoted to a discussion of obstetric pathology under the guidance of Dr. Arthur Hertig. This will be followed by a slide seminar at 7:45 p.m.

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 12. New England Center Hospital House Officers' Association. Page 916, issue of December 4.

DECEMBER 12 AND 13. Association for Research in Nervous and Mental Disease. Page 585, issue of October 9.

DECEMBER 12–22. Springfield Hospital Educational Program. Page 827, issue of November 20.

DECEMBER 12–JANUARY 30. Combined Anesthesia Teaching Conferences of Boston. Page 785, issue of November 13.

DECEMBER 15–17. American Academy of Obstetrics and Gynecology. Page 744, issue of November 6.

DECEMBER 15–MARCH 23. Postgraduate Course in General Medicine. Page 697, issue of October 30.

DECEMBER 17. Lahey Clinic Lectures. Page 698, issue of October 30.

DECEMBER 17–APRIL 8. Postgraduate Medical Institute. Page 452, issue of September 18.

DECEMBER 18. New England Pathological Society. Notice above.

JANUARY 3–JUNE 2. Mount Auburn Hospital Panel Discussions. Page 868, issue of November 27.

JANUARY 13. Springfield Academy of Medicine. Page 916, issue of December 4.

JANUARY 14. Essex North District Medical Society. Page 743, issue of November 6.

FEBRUARY 6. New England Society of Anesthesiologists. Page 827, issue of November 20.

FEBRUARY 9 AND 10. Annual Congress on Medical Education and Licensure. Page 786, issue of November 13.

MARCH 2–5. New Orleans Graduate Medical Assembly. Page 828, issue of November 20.

MARCH 2–MAY 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

APRIL 3. New England Society of Anesthesiologists. Page 418, issue of September 11.

APRIL 29 AND OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

JANUARY 14. Pentucket Club. 111 Main Street, Haverhill.
MAY 13. Andover Country Club, Shawsheen.

MIDDLESEX WEST

DECEMBER 15–MARCH 25. Postgraduate Course in General Medicine.

NORFOLK

JANUARY 27.
FEBRUARY 24.
MARCH 24.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 18

THURSDAY, DECEMBER 18

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. The Surgical Therapy of Pulmonary Tuberculosis. Dr. Norman J. Wilson, Jr. Stearns Auditorium, New England Center Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital. Cambridge.

FRIDAY, DECEMBER 19

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit. 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Dr. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*10:30 a.m.–1:30 p.m. Combined Medical and Surgical Rounds. Stearns Auditorium, New England Center Hospital.
11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
*7:00–9:00 p.m. Combined Anesthesia Teaching Conferences of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street.

SATURDAY, DECEMBER 20

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

(*Notices concluded on page xvii*)